FDA Briefing Document

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

September 12, 2014, 8:00 AM to 5:00 PM

The committee will discuss biologic license application (BLA) 125511, proposed trade name NATPARA (recombinant human parathyroid hormone, 1-84), 25, 50, 75, 100 mcg, lyophilized powder for reconstitution, administered by subcutaneous injection. The proposed indication (use) for this application is replacement for endogenous parathyroid hormone (1-84) for the long-term treatment of hypoparathyroidism. FDA Briefing Document prepared August 14, 2014.

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought BLA 125511 Natpara (recombinant human parathyroid hormone, 1-84) to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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Natpara-Draft Discussion Points

The Natpara clinical program evaluated a once daily dose of up to 100 µg of Natpara in adult patients with hypoparathyroidism due to diverse etiologies (predominantly post-surgical). The REPLACE clinical trial was designed to demonstrate that maintenance of serum calcium levels could be achieved with Natpara using less supplemental calcium and less or no 'active' Vitamin D metabolite/analog. The Natpara clinical program was not designed to evaluate the effect of Natpara on longterm clinical complications of hypoparathyroidism (e.g., nephrocalcinosis, renal impairment, nephrolithiasis, extracellular calcifications, bone fragility, or improvements in health-related quality of life). Changes to short term secondary endpoints thought to be predictive of longterm complications (e.g., 24-hour urinary calcium measurement, bone turnover markers etc.) were measured in the REPLACE trial.

1. Discuss whether the data in the REPLACE trial provides substantial evidence that treatment with Natpara provides clinically meaningful benefit for patients with hypoparathyroidism regardless of etiology. In your discussion specifically address these benefits.

2. Discuss your level of concern with regard to the potential risks (acute and chronic) of hypercalcemia (e.g., titration and maintenance) and hypocalcemia (e.g., withdrawal of therapy) associated with the use of Natpara. Comment on potential ways to mitigate these risks in the clinical setting.

In the dedicated life-long animal toxicology study evaluating the carcinogenic potential of Natpara, a safety signal of bone neoplasms (i.e., osteosarcoma), was observed. This signal was similar to that seen with another PTH product approved for another indication [i.e., Forteo or PTH (1-34)]. The full prescribing information for Forteo includes a boxed warning for this potential risk, recommends against both long term use (>2-years) and use of the product in specific at risk populations.

3. Discuss your level of concern with regard the risk of osteosarcoma associated with long term use of Natpara in patients with hypoparathyroidism. In your discussion, specifically address how similarities and/or differences between the osteoporosis and hypoparathyroidism populations inform or do not inform your assessment of this risk.

4. In light of the overall efficacy and safety findings in the Natpara development program discuss whether the overall risk-benefit of Natpara administered at the doses and regimen proposed supports approval of Natpara for the treatment of hypoparathyroidism.

NPS has developed Natpara, a full-length recombinant human parathyroid hormone (PTH 1-84) as a replacement therapy to treat hypoparathyroidism resulting from inadequate endogenous PTH secretion. PTH (1-84) is synthesized and secreted by the parathyroid glands and is the principal endocrine hormone regulating systemic calcium and phosphorus homeostasis. Physiological actions of PTH include regulation of bone and renal tubular reabsorption of calcium and phosphate, and intestinal calcium absorption. This is mediated through binding to specific high affinity cell surface receptors. In the studies summarized below, PTH 1-84 is known as Natpara and ALX 1-11. PTH 1-34, teriparatide (Forteo) is approved under NDA 21-318 for the treatment of osteoporosis with a high risk of fracture as well as for increasing bone mass.

PHARMACOLOGY

Natpara is identical to endogenous PTH (1-84) and binds PTH-1 receptors in bone, and kidney and indirectly affects calcium reabsorption in the intestine. In bone, PTH liberates calcium by increasing the rate of calcium absorption from the bone by osteocyte/osteoblast mediated osteolysis when administered acutely and by activation of osteoclasts when given chronically. In the kidney, PTH acts on the distal tubule and collecting ducts to increase reabsorption of calcium. PTH increases the conversion of 25-hydroxyvitamin D3 to 1, 25-dihydroxyvitamin D3, which increases absorption of calcium from the intestines. When PTH is delivered intermittently (e.g. once daily) it acts on bone as an anabolic agent by preferentially activating osteoblasts over osteoclasts. This forms the basis of increasing bone mass and strength in osteopenic, ovariectomized female rats and monkeys. This anabolic effect of intermittent PTH exposure contrasts with the net bone catabolism that can occur with continuous exposure to PTH. The stimulatory effects of PTH on osteoblasts are thought to be direct, since these cells express PTH receptors. The stimulatory effect on osteoclasts is thought to be indirect and mediated through osteoblasts. Osteoblasts presumably integrate the strength and duration of the PTH signal in determining whether paracrine activation of osteoclasts will occur. It is important to appreciate that Natpara treatment in hypoparathyroid patients does not mimic physiological conditions in that drug delivery achieves a Cmax of 300 pg/ml whereas the normal PTH range is 15-50 pg/ml. Rats used in the carcinogenicity evaluation were exposed to pharmacologic doses of rh-PTH.

PTH is removed from circulation by the liver and kidney. Kupffer cells in the liver, take up PTH via receptor mediated internalization. PTH is cleaved into N- and C-terminal fragments by peptidases inside these cells. The N-terminal fragment is further degraded within the Kupffer cells while the C-terminal fragments are released back into circulation. The C-terminal fragments of PTH (CPTH) are cleared by the kidney, being hydrolyzed to amino acids during tubular resorption. Because hydrolysis of intact PTH in Kupffer cells occurs more rapidly than renal hydrolysis of the CPTH fragments, the CPTH fragments typically circulate at levels several fold higher than that of full-length PTH.

There is speculation that the CPTH fragments may be biologically active at physiological or pharmacologic exposure, especially in modulating the physiological response to the signal delivered via PTHR1 by PTH 1-84 and by stimulating osteoblast apoptosis (at least in vitro). However CPTH fragments do not compete for binding at the PTHR1 receptor. The existence of a specific CPTH receptor has been hypothesized, but not yet demonstrated.

The osteoblast is the major target cell for PTH in bone. The cell possesses high-affinity surface membrane PTH receptors which are coupled to adenylyl cyclase and phospholipase C. Activation of the two associated signal transduction pathways leads to alterations in osteoblastic function and gene expression. Most likely the anabolic action of PTH on bone is mediated by a combination of intracellular responses triggered specifically by intermittent receptor occupation.

BONE EFFECTS

The overall effect of PTH on bone depends on whether it is administered intermittently or continuously. The intermittent administration of PTH causes an anabolic bone response in animals and in humans. When PTH is administered at closer than daily intervals or infused continuously, the balance shifts and the net response is bone resorption rather than formation. Sustained exposure to PTH activates the osteoblast PTH receptor leading to an indirect paracrine effect on osteoclasts. The result is an increase in bone turnover and a net effect of accelerated bone resorption, increased calcium release, and reduced bone mineral density. However when the increase in PTH 1-84 is transient, bone formation exceeds resorption leading to a marked decreased in bone mineral density at trabecular bone sites (i.e. spine, hip). This anabolic property led to the original development of PTH 1-84 for treatment of postmenopausal osteoporosis.

Hypoparathyroidism differs from osteoporosis in that bone turnover is low and BMD is high, whereas the converse is the case for osteoporosis. Treatment with PTH is expected to improve the biomechanical properties of bone and decrease vertebral fractures in hypoparathyroidism as it does in osteoporosis. The increase in BMD is primarily trabecular bone (i.e. lumbar spine); however BMD decreases primarily at cortical bone sites (i.e. distal radius). The effects of PTH on the skeletal of ovariectomized animal models are relevant to its effect in hypoparathyroidism.

Preclinical and clinical studies have shown that intermittent treatment with PTH injections increases vertebral bone mass and strength. However, the effect of this treatment on non-vertebral, predominantly cortical bone sites is not as clear. Various studies were performed by the sponsor on osteopenic rats and monkeys. In the 18-month monkey bone quality study, daily administration of PTH 1-84 at10 µg/kg/day optimally increased trabecular and cortical bone mass, increased trabecular bone mineral density, improved trabecular bone architecture, quality and strength, and increased cortical bone area/thickness as well as cortical bone strength (work to failure). Similar findings were seen in the 1-year rat bone quality study except that in the rat the

improvement is in cancellous bone. Bone volume was primarily a consequence of increased thickness of existing trabeculae, rather than the formation of new trabeculae as seen in the monkeys. PTH 1-84 improved cortical bone intrinsic strength parameters in the rat, while these parameters worsened in the monkey even while overall cortical bone strength in the monkey remained unchanged as a consequence of increased cortical area. The new bone formed in both species was of normal lamellar structure and there was no evidence of osteoid accumulation or mineralization defects. Neither species exhibited pathologic changes in serum calcium, marrow fibrosis or the presence of abnormal bone cells.

In rats, dose-related increases in bone mass and strength were observed consistently in both trabecular and cortical bone. In monkeys, Natpara treatment improved trabecular microarchitecture and increased bone mass and strength by stimulating new bone formation in both cancellous and cortical bone. In cortical bone it increased Haversian remodeling. While high doses of Natpara decreased cortical bone mineral density (BMD), further analysis showed that bone mineral content was either unaffected or was increased by treatment as was cortical bone strength. At sites containing both trabecular and cortical bone, e.g. femoral neck, Natpara also increased bone strength.

In both rat and monkey, Natpara treatment was associated with increased bone mineral content in trabecular and cortical bone, with a concomitant increase in biomechanical indicators of trabecular bone strength and some biomechanical indicators of cortical bone strength. In monkey, the only cortical bone strength parameter to show improvement was work to failure. In both rat and monkey, improvements in work to failure at cortical sites was primarily a consequence of increased cortical area/thickness. Increases in trabecular bone strength were associated primarily with increased trabecular thickness in the rat and increased trabeculae number in monkey.

Stimulation of new bone formation on trabecular and cortical bone by preferential stimulation of osteoblastic over osteoclastic activity whose mechanism is incompletely understood but thought to involve incomplete differentiation of osteogenic precursor cells (bone lining cells) into osteoblasts and possibly an inhibition of osteoblast apoptosis. The precise mechanism by which PTH exerts this effect has not been elucidated.

TOXICOLOGY

The toxicologic profile of Natpara associated with chronic subcutaneous (SC) dosing has been assessed in the rat and monkey animal models. In both models the primary toxicological targets were the kidney and bone marrow. Post-dose transient hypercalcemia was apparent for 3-6 hours in the monkey at all tested doses, with excursions as high as 1.6 mg/dL (~17% increase) at 10 µg/kg/day (3 times the Maximum Recommended Human Dose; MRHD, based on AUC ratios). Transient serum calcium excursions were not assessed in the rat in the chronic SC dosing study,

but can be inferred from the dose-dependent calciuria that was observed. At toxic doses of Natpara, repetitive kidney exposure to high serum calcium levels resulted in the formation of renal calculi, mineralization, and damage to the renal tubules and occasionally the parenchyma. This was associated with increases in serum alkaline phosphatase and BUN. At the highest dose tested in the rat, 1000 µg/kg/day (100X the MRHD, based upon a mg/m^2 comparison), 30% of the male rats died or were sacrificed moribund. The cause of death/morbidity was determined to be severe kidney damage. All had moderate to severe renal tubular mineralization, and most had calcification of the major vessels, heart and/or stomach. The other consistent toxicological finding with Natpara was a dose-dependent reduction in the level of blood cells (all types) that occurred as a consequence of the exaggerated bone-anabolic effect, which lead to osteosclerosis and occlusion of the marrow space, causing a reduction in blood cell precursors. In the rat, significant increases in blood cells were seen at doses ≥300 µg/kg/day (19 times human AUC at the MRHD).

There is species variability in the sensitivity to PTH-induced renal failure and vascular mineralization with the dog being highly sensitive based on the high capacity of the dog kidney to reabsorb calcium . Thus doses in the dog as low as 9 µg/kg/day (3 times MRHD) causes morbidity in 30% male dogs after 3 doses. Rats are relatively resistant to the pathological effects of hypercalcemia where a NOAEL of 50 µg/kg/day (11 times Human AUC at the MRHD) was established for hypercalcemic renal pathology. The monkey NOAEL was 2 µg/kg/day (less than the human AUC at the MRHD) for renal hypercalcemic associated pathology.

All nonclinical test species developed antibodies to Natpara. However, only a small percentage of test animals developed detectable levels of antibody, and these were generally not neutralizing. Being a native human protein, Natpara is not expected to be highly immunogenic in humans, and animal immunoreactivity is not necessarily predictive of human clinical immune response.

A rat fertility study and both rat and rabbit embryo-fetal developmental toxicity studies found no significant effects outside of the laboratory's range of the historical control variation for measures of fertility, early embryonic development and development of the embryo and fetus following exposure of the pregnant dam from implantation to closure of the hard palate. In a pre- and post-natal development study pregnant rats were administered Natpara during organogenesis until weaning. Effects such as increased morbidity associated with dehydration, broken palate and palate injuries related to incisor misalignment were found in pups from litters given ≥100 µg/kg/day (10 times the 100 µg/day clinical dose based on AUC).

CARCINOGENICITY

In a 2-year rat carcinogenicity study, daily SC dosing of F344 rats with doses of Natpara >50 µg/kg/day were associated with significant increases in the incidence of bone neoplasms,

especially osteosarcomas. The incidence of osteosarcoma in males was 22% at 50 mcg/kg/day (26 times the MRHD, based on AUC ratios) and 45% at 150 µg/kg/day (71 times the MRHD, based on AUC ratios), and somewhat lower in females at 8.3% and 22%, respectively (at 19- and 55-times MRHD based on AUC ratios). Osteoblastomas and osteomas were also increased. The highest dose tested, 150 µg/kg/day (71 times the expected clinical exposure at 100 µg/day), caused significantly increased mortality, especially in males, because of increased osteosarcoma-related mortality. At the lowest tested dose of 10 µg/kg/day, there was no significant increase in bone neoplastic incidence. This dose gave mean exposures in the rat that are 4 times the expected clinical exposure at 100 µg/day at the MRHD. Despite the lack of statistically significant increases in neoplasms in the low dose group, the relatively low safety margin that this dose provides (5 times in males and 3 times in females the clinical exposure at the MRHD of 100 µg/day) does not suggest a negligible risk for developing bone tumors in humans at clinical exposure levels. The Sponsor suggests that this indicates Natpara

has a significantly reduced clinical risk of causing bone tumors compared to teriparatide, as teriparatide is associated with an increase in osteosarcomas (~6%) at 5 µg/kg/day; a dose equivalent to 11µg/kg/day of PTH on a molar basis.

Comparison of Bone Neoplastic Potential of PTH(1-84) and PTH(1-34):

Table 1 -- Incidence (Animals Affected) of Bone Neoplasms in Male F344 Rats: Comparison of ALX1-11 to Teriparatide

	ALX1-11					Teriparatide			
Number examined	60	60	60	60	60	60	60	60	60
Dose Group	C1	C2	LD	MD	HD1*	C	LD	MD	HD
Dose (µg/kg/day)	0	0	10	50	150	0	5	30	75
Exposure Ratio (AUC_{rat}/AUC_{human}**)	-	-	5	26	71	-	3	21	58
Osteoma (n)	0	0	0	1	2	0	0	2	1
(%)	**0**	**0**	**0**	**1.67**	**3.33**	**0**	**0**	**3.33**	**1.67**
Osteoblastoma (n)	0	0	0	2	4	0	0	2	7
(%)	**0**	**0**	**0**	**3.33**	**6.67**	**0**	**0**	**3.33**	**11.67**
Osteosarcoma (n)	0	0	1	13	27	0	3	21	31
(%)	**0**	**0**	**1.67**	**21.67**	**45.00**	**0**	**5.00**	**35.00**	**51.67**
All Bone Neoplasms (n)	1	0	2	17	28	0	3	24	36
(%)	**1.67**	**0**	**3.33**	**28.33**	**46.67**	**0**	**5.00**	**40.00**	**60.00**

*Male HD1 only dosed for 94 weeks and necropsied after 101 weeks.
** AUC_{human} at 100 µg/day= 0.924 ng h/ml (Clinical study C09-002)

Table 2 -- Incidence (Animals Affected) of Bone Neoplasms in Female F344 Rats: Comparison of ALX1-11 to Teriparatide

	ALX1-11					Teriparatide			
Number examined	60	60	60	60	60	60	60	60	60
Dose Group	C1	C2	LD	MD	HD1	C	LD	MD	HD
Dose (µg/kg/day)	0	0	10	50	150	0	5	30	75
Exposure Ratio (AUC_{rat}/AUC_{human}**)	-	-	3	19	55	-	3	21	58

Osteoma (n)	0	0	0	1	1	0	0	0	1
(%)	**0**	**0**	**0**	**1.67**	**1.67**	**0**	**0**	**0**	**1.67**
Osteoblastoma (n)	0	0	0	3	9	0	1	1	3
(%)	**0**	**0**	**0**	**5.00**	**15.00**	**0**	**1.67**	**1.67**	**5.00**
Osteosarcoma (n)	2	0	0	5	13	0	4	12	23
(%)	**3.33**	**0**	**0**	**8.33**	**21.67**	**0**	**6.67**	**20.00**	**38.33**
All Bone Neoplasms (n)	2	0	0	11	20	0	5	13	25
(%)	**3.33**	**0**	**0**	**18.33**	**33.33**	**0**	**8.33**	**21.67**	**41.67**

Table 3 -- Incidence (Animals Affected) of Bone Neoplasms in F344 Rats: Comparison of ALX1-11 to Teriparatide (male & female combined)

	ALX1-11					Teriparatide			
Number examined	120	120	120	120	120	120	120	120	120
Dose Group	C1	C2	LD	MD	HD1*	C	LD	MD	HD
Dose (µg/kg/day)	0	0	10	50	150	0	5	30	75
Exposure Ratio (AUC_{rat}/AUC_{human}**)	-	-	4	23	63	-	3	21	58
Osteoma (n)	0	0	0	2	3	0	0	2	2
(%)	**0**	**0**	**0**	**1.67**	**2.50**	**0**	**0**	**1.67**	**1.67**
Osteoblastoma (n)	0	0	0	5	13	0	1	3	10
(%)	**0**	**0**	**0**	**4.17**	**10.83**	**0**	**0.83**	**2.50**	**8.33**
Osteosarcoma (n)	2	0	1	18	40	0	7	33	54
(%)	**1.67**	**0**	**0.83**	**15.00**	**33.33**	**0**	**5.83**	**27.50**	**45.00**
All Bone Neoplasms (n)	3	0	2	28	48	0	8	37	61
(%)	**2.50**	**0**	**1.67**	**23.33**	**40.00**	**0**	**6.67**	**30.83**	**50.83**

*Male HD1 only dosed for 94 weeks and necropsied after 101 weeks.
**AUC_{human} at 100 µg/day= 0.924 ng h/ml (Clinical study C09-002)

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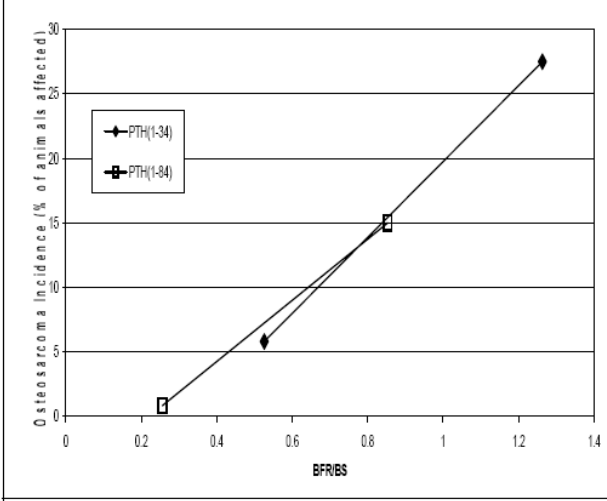
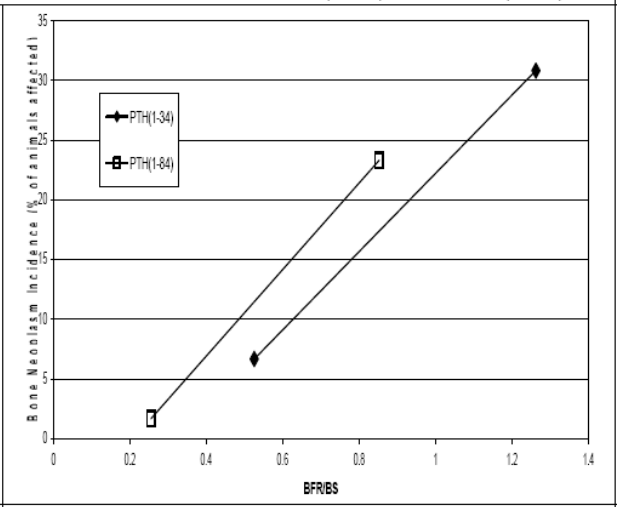
There was no increase in the incidence of osteosarcoma or other bone neoplasms at a dose of 10 µg/kg/day (~4 times the MRHD, based on AUC ratios) when the results are normalized on the basis of human AUC ratios. However, it is likely that the molecular events that are associated with the bone anabolic effects of PTH peptides are the same and when exaggerated, cause osteoblast neoplasia. The differences in the outcomes of the carcinogenicity studies of Natpara and teriparatide may be explained by the drug-related increase in bone formation rate. Then there is little difference between the two peptides (see figure below).

Relationship Between Bone Formation Rate and Bone Tumor Incidence for PTH(1-34) and PTH(1-84)



Osteosarcoma



All Bone Neoplasms

BFR/BS data are from PH-04-025 and combine the BFR/BS values from the proximal tibia metaphysis and lumbar vertebra. Tumor incidence data are from each of the respective 2-year F344 rat carcinogenesis studies.

The Sponsor has suggested that the CPTH fragment of NATPARA is partially protective against bone neoplasia, due its ability to increase apoptosis in osteocytic cells. However, this analysis fails to account for the lower potency of NATPARA when concurrently compared to teriparatide in a bone formation assay conducted in normal 3 month old female F344 rats (Study # PH-04-025). When compared on the basis of molar equivalents, teriparatide is 20-110% more potent than NATPARA, depending upon the particular measurement being compared. On the basis of this realization, analysis was conducted in which the osteosarcoma incidence was normalized by the mean bone formation rate (BFR/BS) measured in study PH-04-025, and found that there is little difference between NATPARA and teriparatide. When the same analysis is extended to all bone neoplasms combined, because of an increase in the incidence of osteoblastoma, Natpara caused more bone tumors per unit forming activity than did teriparatide. When normalized to bone surface area the osteosarcoma incidence for PTH 1-84 and PTH 1-34 are essentially identical.

The sponsor's position that the activity of the C-terminal peptide fragment of PTH (CPTH), acting at the putative CPTH receptor (no such receptor has been purified or cloned), mitigates the pre-neoplastic activity of the N-terminal fragment of PTH, acting at the PTH-1 receptor is not substantiated by data. Furthermore when normalizing the osteosarcoma incidence by a marker of intrinsic activity (i.e. bone formation rate) we found no difference in the bone formation-rate-normalized osteosarcoma incidence between PTH 1-34 and PTH 1-84. While intriguing the CPTH receptor theory lacks substantiation.

CPTH fragments are generated by the liver and released back into circulation. There is some speculation that these fragments may be biologically active at physiological or pharmacological

exposure levels, especially in modulating the physiological response to the signal delivered by PTH-1 receptor by PTH 1-84, however CPTH fragments do not compete for binding at the PTH-1 receptor. The existence of a specific PTH receptor (CPTHR) has been hypothesized based on bimodal Scatchard plots for PTH 1-84 but not PTH 1-34 in cell homogenates from renal cells, and renal and osteosarcoma cell lines. CPTH fragments can compete with radioligand binding to these high capacity, low affinity CPTHR sites. The addition of CPTH fragments to osteosarcoma cell lines has been shown to activate alkaline phosphatase and stimulate the uptake of extracellular calcium. On the basis of these findings the sponsor hypothesizes that PTH 1-84 may be expected to have a unique therapeutic profile compared to other structurally related peptides such as PTH 1-34. It is noteworthy that CPTHR has not been identified or characterized to date so this remains speculative at best. In contrast when concurrently compared in osteopenic OVX rats, PTH 1-84 is a less potent bone anabolic agent than PTH 1-34 consistent with the idea that CPTH fragments negatively modulate the activity of the N-terminal region of PTH. This does not rule out the possibility that the C-terminal portion of PTH 1-84 could negatively affect the potency or efficacy of the N-terminal portion of PTH 1-84 at PTH-1 receptor.

CONCLUSIONS

The toxicology profile of Natpara is consistent with exaggerated pharmacodynamics. The anticipated elevations in serum calcium levels following PTH administration can lead to pathology i.e. renal failure and mineralization of multiple organ systems particular the cardiovascular and GI. The magnitude and duration of the calcium elevation is best correlated with whether or not PTH-induced hypercalcemia results in detectable pathology.

The rat carcinogenicity data indicates a dose-dependent increase in the incidence of bone neoplasms in Natpara treated F344 rats. This effect was similar to that seen with teriparatide (PTH 1-34). There are some numerical differences between the two studies, with Natpara being associated with fewer bone tumors than teriparatide dosing when the tumor incidence is normalized to the AUC exposure ratio between rats and humans. The sponsor has suggested that this is a consequence of the pro-apoptotic activity of CPTH fragments and thus is an indication that Natpara is less likely to cause bone tumors than teriparatide. It is likely that the molecular events associated with the bone anabolic effects of PTH peptides are the same. The differences in the outcomes of the carcinogenicity studies (osteoblast induced neoplasia) may be explained by the lower bone anabolic potency of Natpara. When osteosarcoma incidence is normalized to the drug-related increase in bone formation rate there is little difference between the two peptides. Based on bone forming unit of activity, Natpara and teriparatide have similar potencies

for initiating bone tumor formation in F344 rats. The clinical significance of this ability of PTH peptides to induce bone tumors in rats remains unknown.

Clinical Summary

Biologic Licensing Application (BLA) 125,511

Natpara® (Recombinant Human Parathyroid Hormone, rhPTH [1-84])

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12 September 2014

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Note: Natpara is referred to interchangeably as rhPTH(1-84) and NPSP558 in this document.

I. Introduction

A. Product Description and Proposed Indication

The active ingredient in Natpara is recombinant human parathyroid hormone (rhPTH) identical in primary sequence to the full-length, human, 84-amino acid endogenous hormone. Natpara is not approved in the United States for any indication.

Natpara is packaged in a multiple dose, dual-chamber, glass cartridge in 4 dosage strengths (25, 50, 75, or 100 µg). Natpara is to be self-administered once daily by subcutaneous (SC) injection into the thigh using a reusable pen injector.

NPS Pharmaceuticals (also referred to as the "Applicant") proposes a Natpara starting dose of 50 µg. Up-titration in dose every 2- to 4- weeks to 75 µg and 100 µg can occur if the starting dose does not achieve the desired effect on blood calcium levels. The Applicant also proposes a low dose of 25 µg for patients whose calcium levels remain high with the 50 µg dose.

The Applicant is seeking the following indication for Natpara:

> *Natpara® (rhPTH[1-84]) for injection is a replacement for endogenous parathyroid hormone (1-84) indicated for the long-term treatment of hypoparathyroidism.*

B. Hypoparathyroidism: Pathophysiology and Available Therapies

Endogenous parathyroid hormone is secreted by parathyroid glands in response to low circulating calcium levels and plays an important role in calcium homeostasis.

Hypoparathyroidism is characterized by parathyroid hormone levels insufficient to maintain normal serum calcium levels. It occurs most commonly as a result of accidental (thyroidectomy) or intentional removal of the parathyroid glands (parathyroidectomy) and more rarely in the setting of autoimmune or congenital diseases.

Hypoparathyroidism is a rare disease. A recent survey using a large claims database estimates the number of insured patients in the US with a diagnosis of hypoparathyroidism to be approximately 59,000.[1]

The biochemical abnormalities associated with hypoparathyroidism are those anticipated based on the known physiologic effect of PTH on the kidney and bone, and include hypocalcemia, hyperphosphatemia and hypercalciuria.

The hypocalcemia that results from PTH deficiency is attributed to several mechanisms including reduced absorption of dietary calcium due to reduced Vitamin D activation, increased urinary calcium loss due to decreased urinary calcium reabsorption, and decreased bone turnover through a direct effect on osteoblasts.

The most common symptoms associated with hypoparathyroidism are linked to acute hypocalcemia and are generally reversible with correction of calcium levels. Symptoms associated with acute hypocalcemia include numbness, paresthesia, musculoskeletal irritability (i.e., twitching, tetany, cramps), seizures, cardiac arrhythmias (due to QT prolonging effect), and laryngeal spasms.

Reported chronic complications of hypoparathyroidism include effects that result from chronic hypocalcemia (i.e., cardiomyopathy), effect that results from chronically elevated urinary calcium excretion (i.e., nephrocalcinosis, nephrolithiasis and progressive renal impairment), effects attributed to chronic elevation in blood phosphorus levels (i.e., central nervous system and vascular extracellular calcification), and effects attributed to low bone turnover (i.e., increased bone mass and bone fragility).

There are no FDA approved therapies specifically indicated for hypoparathyroidism. The current standard of care in hypoparathyroidism consists of oral supplementation with calcium and vitamin D. The goal of therapy is to control symptoms while minimizing complications. To this end, therapy aims to maintain serum calcium levels as close to normal as possible without causing hypercalciuria. In practice this may be difficult to achieve because patients with hypoparathyroidism can have hypercalciuria even at serum calcium levels in the low normal range owing to the absence of PTH's effects on urinary calcium reabsorption. Treatment guidelines advocate targeting a serum calcium

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1 Powers J et al. Prevalence and incidence of hypoparathyroidism in the United States using a large claims database. Journal Bone Mineral Research December 2013.

range of 8-9 mg/dL, a 24-hour urine calcium excretion below 300 mg/24 hr, and a calcium-phosphate product below 55.

Achieving therapeutic goals often involves intake of daily calcium doses that exceed one gram per day, coupled with administration of either high-dose 25-hydroxyvitamin D or replacement doses of 1, 25-dihydroxyvitamin D. These therapies maintain serum calcium by increasing intestinal calcium absorption. Thiazide diuretics are used in an attempt to reduce urinary calcium excretion.

C. Limitations of Current Therapies

The standard treatment of hypoparathyroidism with calcium and vitamin D is less than optimal. For patients who require large doses of calcium to maintain normocalcemia, the intake of numerous supplements multiple times daily may represent an inconvenience and may cause gastro-intestinal tolerability issues (e.g., constipation). Adjustment of serum calcium using supplemental calcium and vitamin D is imprecise. As was stated above, achieving a reasonable balance between maintenance of serum calcium without causing hypercalciuria is challenging. Under-treatment may result in acute or chronic hypocalcemia. Overtreatment may result in acute hypercalcemia, chronic hypercalcemia and hyperphosphatemia which may result, in some patients, to precipitation of calcium phosphate in soft tissues, including the kidneys, heart, and brain.

As was stated above, patients with hypoparathyroidism are predisposed to kidney stones, nephrocalcinosis and renal impairment due to chronic hypercalciuria. Although diuretics are used to address this problem, these do not correct the underlying renal calcium handling abnormality, and the efficacy of diuretics to prevent the long-term above listed renal complications is unclear.

Finally, treatment of hypoparathyroidism with calcium and vitamin D does not address the defective bone metabolism resulting from PTH deficiency, which leads to chronically low bone turnover which may result in poor bone quality.

D. Approved Product with Related Safety Concern

Forteo is a recombinant, truncated version of the full length human hormone containing the first 34 amino acids of endogenous PTH. It was approved in 2002 and is indicated[2] for:

- The treatment of postmenopausal women with osteoporosis at high risk for fracture
- To increase of bone mass in men with primary of hypogonadal osteoporosis at high risk for fracture; and
- For the treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture.

The Package Insert (PI) for Forteo includes a boxed warning for the potential risk of osteosarcoma. This risk was identified based on observations of significant increases in the incidence of bone neoplasms (especially osteosarcoma), at clinically relevant exposure, in 2-year rodent carcinogenicity studies (i.e., life-long animal studies). A summary of similarities and differences in the carcinogenic potential of Forteo and Natpara are discussed in a separate FDA review in this backgrounder (refer to the Agency's Non-clinical Review).

To mitigate this potential risk, the full prescribing information (FPI) for Forteo[3]

- Recommends against the use of Forteo in patients at increased baseline risk of osteosarcoma (e.g., patients with Paget's disease, young adults with open epiphyses, and patients with a history of skeletal radiation).
- Recommends limiting Forteo treatment duration to a maximum of two years.
- Recommends against the use Forteo in patients with a history of skeletal metastasis or malignancies
- Recommends against the use of Forteo in metabolic bone disease other than osteoporosis

[2] Forteo Full Prescribing Information, Revised 3/2012

3 Forteo Full Prescribing Information, Revised 3/2012. See Warning and Precautions 5.1 to 5.4.

E. Regulatory History for rhPTH (1-84)

NPS pharmaceuticals developed rhPTH (1-84) under the trade name Preos for the treatment of osteoporosis in post-menopausal women at high risk of bone fracture. A new drug application was submitted for this indication in May 2005. The Agency did not authorize marketing of Preos, and the applicant was asked to address two safety concerns identified in the application before Preos could be marketed for this indication. First, the applicant was asked to address the observation of significant hypercalcemia associated with the proposed daily dosing regimen (100 µg per day co-administered with calcium and Vitamin D) in pivotal trials to support the osteoporosis indication. Second, the applicant was asked to address safety issues related to the reliability and use of the proposed to-be commercialized device. The Applicant withdrew the NDA for this indication in 2011. The data obtained in the osteoporosis population was judged of limited value to informing the benefit risk for the hypoparathyroidism indication and will not be discussed in this backgrounder unless relevant. The risk of hypercalcemia in the hypoparathyroidism population was directly assessed in this program and is discussed below. With regard to the device reliability issues, the applicant has proposed marketing a new device for the hypoparathyroidism indication.

The Investigational New Drug (IND) Application for the hypoparathyroidism indication was opened in 2006 and the product received Orphan Drug Designation in 2007.

II. Natpara Clinical Trials in Hypoparathyroidism

A. Overview

The Natpara clinical development program includes 4 safety and efficacy trials. Among them, Study CL1-11-040 (REPLACE) stands as the only placebo-controlled, Phase 3 trial, and is considered the “pivotal” trial for this submission; all other studies are considered as providing supportive data, as some are open-label and lack control arms, while others are shorter and enroll fewer patients. Because of important differences in trial design, data from different trials are not pooled, and they are discussed separately.

Trials most relevant to the efficacy and safety of rhPTH(1-84) for the treatment of hypoparathyroidism are summarized in the Table below. Subjects were allowed to participate in more than one trial sequentially.

Table 1 NPS Efficacy and Safety Studies in Hypoparathyroidism

Study	Objectives	Design/Control	Dose	# Subjects	Duration
CL1-11-040 (REPLACE)	Efficacy and safety	Randomized, double-blind, placebo-controlled	50, 75, and 100 µg (flexible doses) or placebo	rhPTH(1-84), 90; placebo, 44	24 weeks
PAR-C10-007 (RELAY)	Efficacy and tolerability	Randomized, dose-blinded	25 or 50 µg (fixed doses)	25 µg, 23; 50 µg, 24	8 weeks
PAR-C10-008 (RACE)	Safety and tolerability	Open-label	25, 50, 75, and 100 µg (flexible doses)	53	52 weeks + extension ONGOING
PAR-C10-009 (REPEAT)	Safety and tolerability	Open-label	50, 75, and 100 µg (flexible doses)	24	24 weeks

This review will discuss primarily the data from the pivotal trial (REPLACE). Trials 007 (RELAY) and 008 (RACE) provided efficacy and safety information that was consistent with the REPLACE trial data, and they are presented to provide important supportive information. Trial 009 (REPEAT) was a small, single-center study, and data from that trial does not greatly enhance the discussion of Natpara.

B. Significant Issues Related to Good Clinical Practices (GCP)

FDA inspected three clinical sites that contributed data to this Biological Licensing Application (BLA). One of the sites was noted to have multiple and significant GCP violations across several trials in the program, including the pivotal trial. The violations raised significant questions regarding the adequacy of trial conduct at that site. In light of these violations FDA determined that data originating from this site was unreliable. Data from two other inspected sites was considered adequate. FDA excludes data from the site whose data was deemed unreliable in the backgrounder and presentations. For the pivotal trial, this led to the exclusion of 4 placebo- and 6 Natpara-treated subjects (originally 44 and 90 subjects, respectively; after exclusion: 40 and 84 patients, respectively).

C. Pivotal Trial (040, or REPLACE)

Please note that, unless otherwise specified, serum calcium and albumin-corrected total serum calcium are used interchangeably in this review.

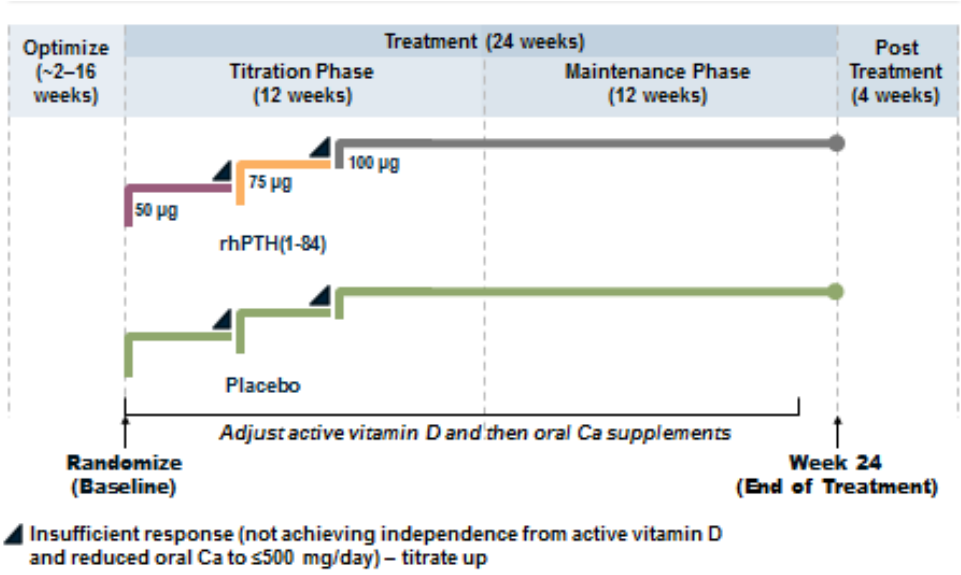
The objective of this trial was to evaluate safety and efficacy of NPSP558 compared with placebo in adults with hypoparathyroidism receiving current standard of care treatment that consisted of calcium and active Vitamin D/Vitamin D analog supplements.

Study Design

REPLACE was a randomized, double-blind, placebo-controlled, international (33 sites in 8 countries; 20 sites in the US), 6-month, Phase 3 clinical trial. Consistent with FDA recommendations made in 2007, NPS evaluated Natpara as add-on therapy to the standard of care, and the trial was designed to evaluate whether Natpara 50 µg, 75 µg or 100 µg administered as a single daily dose could reduce or replace oral calcium and Vitamin D for the treatment of hypoparathyroidism.

The overall REPLACE schematic is depicted in the figure below. The trial consisted of a screening and stabilization period, collectively referred to as the optimization period, a treatment phase and an end of treatment follow-up phase.

Figure 1: Scheme for Trial 040



From Applicant's Clinical Study Report

Optimization Period

The goal of the optimization period was to standardize calcium and Vitamin D supplementation, normalize 25-hydroxyvitamin D levels, and achieve a stable baseline serum calcium level prior to randomization.

In the optimization phase doses of calcium supplements (calcium citrate) and active Vitamin D/Vitamin D analogs (calcitriol in the US and alphacalcidol in Europe) were adjusted to target a serum calcium level of 8 to 8.5 mg/dL (slightly below the normal range). Those with serum 25(OH) vitamin D levels below the lower limit of normal at screening were supplemented with vitamin D_3 (2000 IU/day) until serum 25(OH) vitamin D levels returned to the normal range (30 ng/mL considered LLN).

Magnesium supplementation (for patients with low magnesium levels), and discontinuation of thiazide diuretics also occurred if needed prior to randomization.

Randomization and Treatment Period

Following optimization, subjects who met specific criteria[4] were randomized 2:1 to NPSP558 or placebo once daily and entered the 24-weeks treatment phase. The treatment phase divided into a 12-week titration phase and a 12-week dose maintenance phase. The titration period involved up-titration of study drug and concomitant down-titration/elimination of calcium and active vitamin D metabolite/analog.

End of Treatment and Washout Period

At the end of treatment, subjects discontinued randomized therapy and entered a 4-week post-treatment follow-up period during which patients returned to pre-enrollment oral supplementation.

Dosing and Titration

One of the stated goals of the trial was to "to reduce the need for active vitamin D metabolite/analog treatment to the maximum degree clinically possible and to decrease

4 Daily calcium citrate dose was 1,000 mg or greater and the daily dose of calcitriol was 0.25 µg greater, or the daily alphacalcidol dose was 0.50 µg or greater. Two successive study visits separated by a 2-week interval were characterized by: no more than a 25% change in the daily doses of both calcium, citrate and active vitamin D/Vitamin D analog; the second of 2 serial albumin-corrected total serum calcium concentrations was higher or comparable to the prior albumin-corrected total serum calcium value; the albumin-corrected total serum calcium concentration was between 7.5 mg/dL and the ULN.

the prescribed oral calcium supplementation ideally to as low as possible" during dosing and titration of Natpara.

This required coordinated titration of three therapeutic agents: calcium, active Vitamin D /Vitamin D analog, and Natpara (or placebo). Titration decisions were to be guided by albumin-corrected serum calcium levels and the goal was to achieve a target calcium range of 8-9 mg/dL (i.e., the lower half of the normal reference range). This target calcium range was maintained throughout the trial.

Dosing Recommendation at Randomization

At randomization Natpara (or placebo) was started at a dose of 50 µg and the dose of active Vitamin D metabolite/analog was cut by 50% to mitigate against the risk of hypercalcemia.

Dosing Adjustment Recommendations during Treatment Period

Downward titration of supplemental calcium and active Vitamin D metabolite/analog was to continue provided serum calcium remained at target until all supplements except for 500 mg/day of oral calcium supplement were discontinued.

Up-titration of Natpara (or placebo) to 75 mg and 100 mg took place at the end of the first and fourth week of treatment, respectively, in subjects who had not achieved independence from active vitamin D/Vitamin D analog and had not reduced oral calcium supplementation to 500 mg/day or less on the previous Natpara dose.

The titration scheme was however flexible and ultimately left at the discretion of the Investigator.

These general principles of titration were delineated in a protocol-specified algorithm that investigators were expected to follow while exercising at the same time their best clinical judgment. The algorithm, however, was quite complex, and adjustment of any of the three therapeutic agents (Natpara, calcium, active vitamin D/Vitamin D analog) was dependent on specific ranges of serum calcium (see footnote for a specific example).[5]

5 As an example, the guideline states that at Week 1 of treatment, if serum calcium was 8-9 mg/dL, no changes in any supplements would be made. If calcium was <8 mg/dL, oral supplemental calcium was to be increased by 25%. If serum calcium was 9.1-10.5 mg/dL, the following were options: 1) remaining vitamin D should be eliminated; if subject is no longer receiving vitamin D then reduce oral calcium by 25-50%; if serum calcium is 9.1-9.5 mg/dL, reduce oral calcium by 25%; if serum calcium is 9.6-10,5 mg/dL, reduce oral calcium by 50%; iIf the serum calcium was 10.6-11.9 mg/dL, vitamin should be withdrawn and oral calcium reduced by 50%.

If at any time in the trial serum calcium deviated from the 8-9 mg/dL goal, upward or downward adjustments in active Vitamin D metabolite/analog dose and/or oral calcium as appropriate, were allowed.

If hypercalcemia persisted despite maximal down-titration of supplements, the dose of Natpara could be reduced. If the serum calcium concentration remained above the upper limit of normal (ULN) for 2 or more assessments at the lowest drug level following withdrawal of all supplementary calcium and active vitamin D metabolite/analog, the subject could be discontinued.

Inclusion and Exclusion Criteria

The study enrolled adult patients with hypoparathyroidism confirmed for 18 months or longer and who required both calcium and active Vitamin D/Vitamin D analog supplements. Importantly, it excluded hypoparathyroidism due to calcium sensing receptor mutations. Specific inclusion and exclusion criteria for REPLACE are listed below:

***Key Inclusion Criteria**:*

1) Male and female adults ages 18 to 85 years
2) History of hypoparathyroidism for ≥18 months, including historical biochemical evidence of hypocalcemia and concomitant serum intact PTH concentrations below the lower limit of normal of 2 test dates at least 21 days apart within 12 months prior to randomization
3) Requirement for vitamin D metabolite/analog therapy with calcitriol ≥0.25 µg per day or alphacalcidol ≥0.50 µg per day prior to randomization
4) Requirement for supplemental oral calcium treatment ≥1000 mg per day over and above normal dietary calcium intake
5) Normal thyroid function tests. For subjects on thyroid replacement therapy, the dose must have been stable for at least 3 months prior to screening
6) Normal serum magnesium levels at the end of optimization period
7) Serum 25-hydroxyvitamin D level ≤1.5-fold the laboratory ULN at the end of the optimization period. Subjects with low levels at screening underwent supplementation with vitamin D during the optimization period. Subjects with levels above the ULN had vitamin D supplements withdrawn during the optimization period. Normal levels were confirmed by the end of the optimization period

8) Creatinine clearance >30 mL/min on 2 separate measurements OR creatinine clearance >60 mL/min and serum creatinine <1.5 mg/dL by the end of the optimization period
9) Women were required to either be post-menopausal or have a negative pregnancy test and use 2 medically acceptable methods of contraception with a pregnancy test scheduled at each visit.

Key Exclusion Criteria:

1) Known history of hypoparathyroidism resulting from an activating mutation in the *CaSR* gene or impaired responsiveness to PTH (pseudohypoparathyroidism)
2) Any disease that may affect calcium metabolism or calcium-phosphate homeostasis, including active hyperthyroidism, Paget's disease, Type 1 and poorly controlled Type 2 diabetes mellitus (HbA1c>8%), severe and chronic cardiac, liver or renal disease, Cushing's syndrome, neuromuscular disease, myeloma, pancreatitis, malnutrition, rickets, recent prolonged immobility, active malignancy, primary or secondary hyperparathyroidism, a history of parathyroid carcinoma, hypopituitarism, acromegaly, or multiple endocrine neoplasia types I and II
3) Subjects with a history of thyroid cancer must have been documented to disease-free for a period of at least 5 years
4) Dependent on regular parenteral calcium infusions to maintain calcium homeostasis
5) Subjects who have undergone gastric resection or have active peptic ulcer disease requiring medical therapy
6) Use of prohibited medication such as loop and thiazide diuretics, raloxifene hydrochloride, lithium, estrogens and progestins for replacement therapy, methotrexate, or systemic corticosteroids within respective prohibited period.
7) Use of other drugs known to influence calcium and bone metabolism, such as calcitonin, fluoride tablets, or cinacalcet hydrochloride within the prohibited period
8) Use of oral bisphosphonates within the previous 6 months or IV bisphosphonate preparations within the previous 12 months prior to screening
9) Previous treatment with PTH-like drugs, including PTH(1-84), PTH(1-34) or other N-terminal fragments or analogs of PTH or PTH-related protein within 6 months prior to screening
10) Seizure disorder/epilepsy with a history of seizure within the previous 6 months prior to screening

11) Presence of open epiphyses
12) Radiotherapy within 5 years
13) Serum 25-hydroxyvitamin D levels greater than 1.5-fold the ULN prior to randomization
14) Pregnant or lactating women
15) Clinical history of renal stones within the past 12 months
16) History of gout
17) Diseases that adversely affect gastrointestinal absorption, including short bowel syndrome, bowel resection, tropical sprue, celiac disease, ulcerative colitis, and Crohn's disease
18) Chronic/severe cardiac disease
19) History of cerebrovascular accident

Primary Efficacy Measure:

The primary efficacy measure was the proportion of patients who met all three components of a composite of three endpoints at Week 24. The composite included the following 3 components:

- At least a 50% reduction from the baseline oral calcium supplementation dose (investigator reported) **and**
- At least a 50% reduction from the baseline active vitamin D metabolite/analog dose (investigator reported) **and**
- An albumin-corrected total serum calcium concentration that was maintained or normalized compared to the baseline value (≥7.5 mg/dL) and did not exceed the upper limit of normal

Changes to the albumin-corrected total serum calcium component were made in Protocol Amendment 7 while the REPLACE study was ongoing. This change is discussed in detail in the Protocol Amendment section of this review.

Secondary supportive efficacy measures discussed in this document include:

- percent reduction in calcium supplementation dose at Week 24
- proportion of subjects who achieved independence from supplemental active vitamin D metabolite/analog usage and a calcium supplementation dose of ≤500 mg/day by Week 24

There was an additional secondary endpoint entitled "the frequency of clinical symptoms of hypocalcemia (including paresthesia, muscle cramping, tetany, seizures) during Weeks 16 to Week 24." This endpoint is not discussed in this document because it departs from the blinded evaluation of adverse events that is provided in the trial (the Applicant provides an interpretative analysis based on *post hoc* input from experts). We believe that the hypocalcemia data are more objectively captured by the unmodified comparisons of adverse event frequencies in the original datasets of this placebo controlled trial.

Exploratory endpoints discussed in this document include:

- change from baseline in 24-hour urine calcium excretion at Week 24
- proportion of patients that maintain a calcium –phosphate product in the normal range of 35-55 mg^2/dL^2 at Week 24 in the NPSP558 treatment group vs. placebo
- change in bone mineral density (BMD) as measured by DXA at Week 24
- change in bone turnover markers at Week 24

The Original Protocol included the following as secondary endpoints: "maintenance of calcium-phosphorus product in the normal range" and "proportion of patients who achieve a 24 hour urinary calcium level below 300 mg at Week 24 in the NPSP558 treatment group vs. placebo." Both endpoints were changed to exploratory endpoints before unblinding.

Population Used in the Primary and other Analyses

Efficacy analyses were conducted for the following patient populations: Intent-to-treat (ITT), which includes all randomized subjects who received at least 1 dose of study drug and had at least 1 post-baseline efficacy measurement, and per-protocol (PP), which was a subset of the ITT population who had no significant protocol violations.

Safety Measurements

These included monitoring of AEs, clinical evaluations (vital signs, physical exams, and EKGs), and laboratory tests (hematology, chemistry, creatinine clearance, urinary biochemistry, immunology, urinalysis, BMD). Safety analyses were conducted in the Safety Population, which includes all randomized subjects who received at least 1 dose of study drug with any follow-up information.

Protocol Amendments

There were several protocol amendments in this trial, one of which, Amendment 7, requires further discussion because it changed the definition used to define the primary efficacy measure. In the original protocol, the third component of the primary composite endpoint was defined as *"patients should have a clinically stable serum calcium level that is established to the satisfaction of the Investigator at Baseline and is maintained or normalized by Week 24 of the study. At the end of the treatment phase it is aimed that patients should have a serum calcium level that is clinically stable in the opinion of the Investigator and just below or within the lower half of the normal range."* This description is somewhat inconsistent because it refers both to a "normalized" serum calcium and to a "below or within the lower half of the normal range" "serum calcium at week 24.

In Amendment 7, approximately 16 months after original protocol submission, the third component of the primary endpoint was changed to: "*an albumin-corrected total serum calcium concentration that is normalized or maintained compared to the baseline value (≥7.5 mg/dL) and does not exceed the upper limit of the laboratory normal range."* This description re-defines the third component of the primary efficacy endpoint as subjects with serum calcium between 7.5 mg/dl and the upper limit of normal (10.6 mg/dl). The impact of this change on the primary endpoint analysis is assessed in the efficacy section of this briefing package.

When Amendment 7 was introduced 7 out of 124 subjects had been randomized, and 22 out of 124 at the time Amendment 7 implementation was complete at all study sites.

III. Efficacy Results: Trial CL1-11-040 (REPLACE)

A. Demographics and Baseline Characteristics

Demographics and baseline characteristics for subjects randomized in the pivotal trial are presented in the tables below.

Overall, demographics were similar between the two groups. The mean age for all subjects was 47.3 years. The majority of subjects were female (79%) and white (96%).

Subjects in the NPSP558 group had hypoparathyroidism for a mean of 14.6 years at the time of enrollment, compared to 11.6 years in the placebo group. The majority of subjects (47.6 % overall) had hypoparathyroidism for over 10 years. Most subjects took 2000 mg of calcium or less daily (69.4%).

Table 2 Demographics and General Baseline Characteristics in Trial 040—All Subjects Randomized

Variable	Placebo N=40 n (%)	NPSP558 N=84 n (%)	Total N=124 n (%)
Age (years)			
Mean (SD)	48.9 (13.7)	46.6 (12.2)	47.3 (12.7)
Median	52	47.0	48.5
Min, Max	21, 73	19, 74	19, 74
Age Category			
<45 years	13 (32.5)	35 (41.7)	48 (38.7)
45 to 64 years	23 (57.5)	45 (53.6)	68 (54.8)
≥65 years	4 (10)	4 (4.8)	8 (6.5)
Gender[a]			
Female	33 (82.5)	65 (77.4)	98 (79)
Male	7 (17.5)	19 (22.6)	26 (21)
Race			
White	39 (97.5)	80 (95.2)	119 (96)
Black	0	1 (1.2)	1 (0.8)
Asian	1 (2.5)	1 (1.2)	2 (1.6)
Native Hawaiian/Pacific Islander	0	1 (1.2)	1 (0.8)
Other	0	1 (1.2)	1 (0.8)
Ethnicity			
Hispanic or Latino	0	2 (2.4)	3 (2.2)
Not Hispanic or Latino	40 (100)	82 (97.6)	122 (98.4)
Body mass index (kg/m^2)			
Mean (SD)	28.9 (5.3)	29.2 (6.4)	29.2 (6.1)
Median	29.6	29.1	29.2
Min, Max	18.2, 38.9	18.9, 48.4	18.2, 48.4
Geographic Region of Enrollment			
North America	21 (52.5)	43 (51.2)	64 (51.6)
Western Europe	12 (30)	25 (29.8)	37 (29.8)
Central and Eastern Europe	7 (17.5)	16 (19)	23 (18.5)

[a] Subject 1007-003 had gender transformation before study enrollment.

From Applicant Submission dated May 27, 2014, Table B-14.1.2.1

Table 3 Baseline Characteristics Related to Hypoparathyroidism in Trial 040—All Subjects Randomized

Variable	Placebo N=40 n (%)	NPSP558 N=84 n (%)	Total N=124 n (%)
Duration of hypoparathyroidism (years)			
Mean (SD)	11.6 (8.1)	14.6 (11.2)	13.6 (10.3)
Median	8.5	10.5	9

Min, Max	2, 38	2, 50	2, 50
Duration of hypoparathyroidism			
≤ 5 years	10 (25)	15 (17.9)	25 (20.2)
> 5-10 years	13 (32.5)	27 (32.1)	40 (32.3)
> 10 years	17 (42.5)	42 (50)	59 (47.6)
Prescribed active vitamin D metabolite/analog at baseline[a]			
Low dose	3 (7.5)	6 (6.7)	10 (7.5)
Medium dose	12 (30)	23 (25.6)	35 (26.1)
High dose	25 (62.5)	61 (67.8)	89 (66.4)
Prescribed calcium at baseline			
0-2000 mg/day	29 (72.5)	57 (67.9)	86 (69.4)
>2000 mg/day	11 (27.5)	27 (32.1)	38 (30.6)

[a] For calcitriol: low dose 0-0.25 µg/day, medium dose >0.25-0.5 µg/day, high dose >0.5 µg/day; for alphacalcidol: low dose 0-0.50 µg/day, medium dose >0.50-1.0 µg/day, high dose >1.0 µg/day

From Applicant Submission dated May 27, 2014, Table B-14.1.2.1

Table 4 categorizes subjects by etiology of hypoparathyroidism, including whether the disease was of childhood or adult-onset. In both groups, adult-onset hypoparathyroidism was overwhelmingly more common (95% and 83% of placebo and NPSP558 subjects, respectively). Among adults, post-surgical was the most-common general etiology, with thyroidectomy being the most common surgery to have resulted in the deficiency. Idiopathic hypoparathyroidism was the next most frequent etiology and accounted for one-fifth to one-fourth of cases.

Table 4 Summary of Etiology of Hypoparathyroidism—All Subjects Randomized CL1-11-040

	Placebo N=40			NPSP558 N=84		
Etiology	Childhood n (%)	Adult n (%)	All Age n (%)	Childhood n (%)	Adult n (%)	All Age n (%)
Post-Surgical	0	29 (72.5)	29 (72.5)	5 (6)	55 (65.5)	60 (71.4)
Thyroidectomy	0	28 (70)	28 (70)	4 (4.8)	51 (60.7)	55 (65.5)
Automimmune	0	1 (2.5)	1 (2.5)	0	0	0
Thyroiditis	0	4 (10)	4 (10)	2 (2.4)	6 (7.1)	8 (9.5)
Basedow's Disease	0	4 (10)	4 (10)	0	7 (8.3)	7 (8.3)
Goiter	0	0	0	0	1 (1.2)	1 (1.2)
Larynx Cancer	0	0	0	0	1 (1.2)	1 (1.2)
Thalassemia	0	7 (17.5)	7 (17.5)	1 (1.2)	18 (21.4)	19 (22.6)
Thyroid Cancer	0	12 (30)	12 (30)	1 (1.2)	18 (21.4)	19 (22.6)
Unknown	0	1 (2.5)	1 (2.5)	1 (1.2)	4 (4.8)	5 (6)
Parathyroidectomy						
Autoimmune Hypoparathyroidism	0	1 (2.5)	1 (2.5)	1 (1.2)	0	1 (1.2)
Di George Syndrome	1 (2.5)	0	1 (2.5)	2 (2.4)	0	2 (2.4)
Idiopathic Hypoparathyroidism	1 (2.35)	8 (20)	9 (22.5)	6 (7.1)	15 (17.9)	21 (25)
Total	2 (5)	38 (95)	40 (100)	14 (16.7)	70 (83.3)	84 (100)

From Applicant's Submission dated May 30, 2014, Table 1b

There were small differences between screening (trial enrolment) and baseline (randomization) of certain laboratory parameters and oral supplement doses. This reflects the optimization period, during which doses of supplements were adjusted to achieve a specific target serum calcium concentration (8-9 mg/dL). Some of these parameters are summarized below. It is notable that the mean 24-hour urine calcium increased from screening to baseline, perhaps in part reflecting the increase in calcium supplementation recorded.

Table 5 Summary of Supplements and Selected Laboratory Assessment at Screening and Baseline—All Subjects with Both Screening and Baseline Data

Variable	Screening N=124	Baseline N=124
Active Vitamin D metabolite/analog (µg)		
n	124	124
Mean (SD)	1 (0.8)	0.9 (0.4)
Median	0.8	0.8
Min, Max	0.3, 4.3	0.3, 2
Calcium Supplement (mg)		
n	124	124
Mean (SD)	2074 (1581)	2108 (1321)
Median	1500	2000

Min, Max	500, 12000	1000, 12000
Total Serum Calcium (mmol/L)		
n	123	123
Mean (SD)	2.1 (0.3)	2.2 (0.2)
Median	2.1	2.2
Min, Max	1.2, 3.1	1.4, 2.9
Serum 25-Hydroxyvitamin D (ng/mL)		
n	120	120
Mean (SD)	41.9 (25.9)	43.1 (16.3)
Median	34	38
Min, Max	8, 150	11, 109
Serum 1,25-Dihydroxyvitamin D (pg/mL)	99	
n	30.8 (19.4)	99
Mean (SD)	26	33.8 (19.8)
Median	9, 148	30
Min, Max		9, 148
24-Hour Urine Calcium (mg/24 hr)	100	
n	267.8 (175.88)	100
Mean (SD)	227.30	343.76 (181.09)
Median	17.20, 803	320.60
Min, Max		26, 973

From Applicant's Submission dated May 28, 2014, Table B-14.4.5

The following table summarizes baseline medical conditions for both groups. This summary only includes conditions present in at least 9% in either group. In general, there were no clinically important differences between the two groups.

Table 6 Summary Baseline Medical History for Conditions Present in ≥9% in Either Group

Preferred Term	**Placebo (N=40) n (%)**	**rhPTH (1-84) (N=84) n (%)**	**Total (N=124) n (%)**
Hypoparathyroidism	38 (95)	82 (97.6)	120 (96.8)
Thyroidectomy	27 (67.5)	52 (61.9)	79 (63.7)
Hypothyroidism	22 (55)	42 (50)	64 (51.6)
Hypertension	10 (25.0)	29 (34.5)	39 (31.5)
Seasonal Allergy	6 (15)	18 (21.4)	24 (19.4)
Thyroid Cancer	6 (15)	19 (22.6)	25 (20.2)
Drug Hypersensitivity	7 (17.5)	13 (15.5)	20 (16.1)
Gastroesophageal Reflux Disease	7 (17.5)	9 (10.7)	16 (12.9)
Depression	7 (17.5)	7 (8.3)	14 (11.3)
Goiter	7 (17.5)	7 (8.3)	14 (11.3)
Hysterectomy	4 (10)	10 (11.9)	14 (11.3)
Appendectomy	8 (20)	6 (7.1)	14 (11.3)
Menopause	7 (17.5)	6 (7.1)	13 (10.5)

Migraine	5 (12.5)	8 (9.5)	13 (10.5)
Tonsillectomy	7 (17.5)	5 (6)	12 (9.7)
Basedow's Disease	4 (10)	8 (9.5)	12 (9.7)
Cholecystectomy	3 (7.5)	8 (9.5)	11 (8.9)
Nephrolithiasis	2 (5)	8 (9.5)	10 (8.1)
Cataract	2 (5)	8 (9.5)	10 (8.1)
Obesity	4 (10)	6 (7.1)	10 (8.1)
Hypercholesterolemia	5 (12.5)	3 (3.6)	8 (6.5)
Osteoarthritis	5 (12.5)	2 (2.4)	7 (5.6)
Fibromyalgia	4 (10)	2 (2.4)	6 (4.8)
Hypocalcemia	4 (10)	2 (2.4)	6 (4.8)
Insomnia	4 (10)	2 (2.4)	6 (4.8)

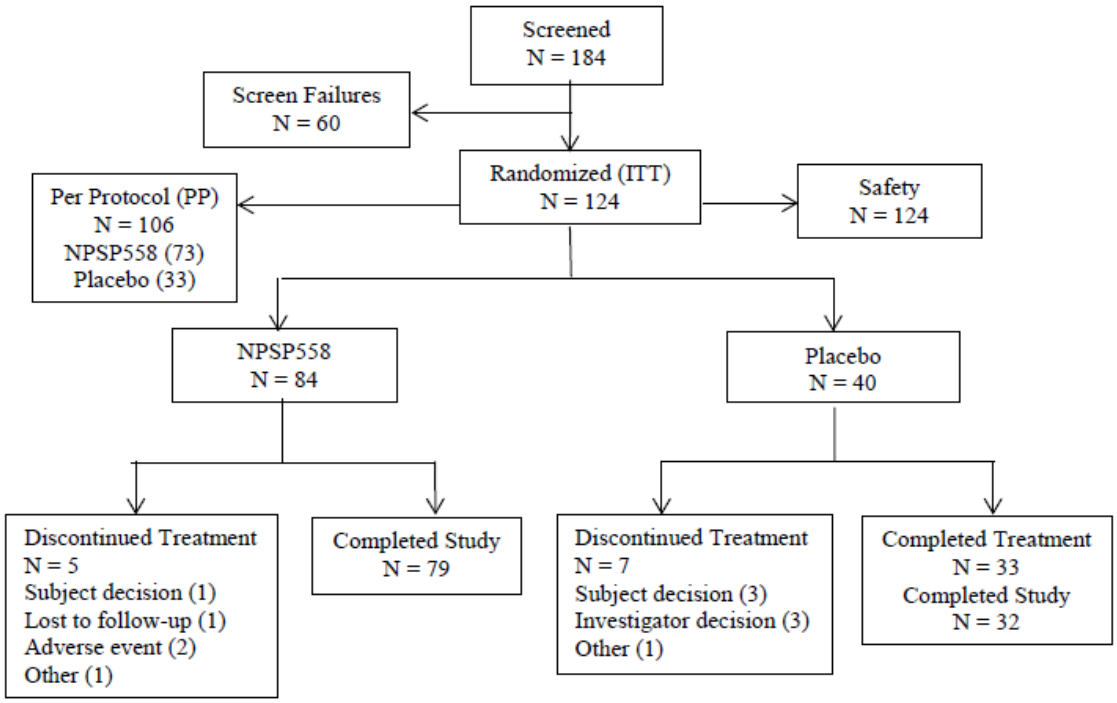
From Applicant's Submission Dated May 30, 2014, Table 3b

There were no clinically important differences between the two groups in baseline concomitant medications. Approximately 89% of total subjects took vitamins and 55% took mineral supplements (excluding calcium and vitamin D analogs) and 70% were on thyroid hormone therapy.

B. Subject Disposition

A total of 32 sites in 8 countries (USA 19, Canada 3, Denmark 3, Hungary 3, Belgium 1, France 1, Italy 1, UK 1) screened 184 subjects and randomized 124 subjects, 80 to NPSP558 and 40 to placebo (eventually only twenty-eight sites randomized subjects because sixty subjects failed screening).

Figure 2 Subject Disposition—All Subjects



From Applicant's Submission dated May 29, 2014, Figure 10-1

The table below summarizes the study analysis populations.

Table 7 Summary of Study Analysis Populations

	Placebo n (%)	**rhPTH(1-84) n (%)**	**Total n (%)**
Randomized	40	84	124
Intent-to-Treat	40 (100)	84 (100)	124 (100)
Per-Protocol	33 (82.5)	73 (86.9)	106 (85.5)
Safety	40 (100)	84 (100)	124 (100)
Completed Treatment	33 (82.5)	79 (94)	112 (90.3)
Completed Treatment plus Follow-Up	32 (80)	79 (94)	111 (89.5)

The following table summarizes subject disposition for the all randomized population. Study completion was high for the NPSP558 arm (94%) and somewhat lower for the placebo group (82%). Most patient discontinuations were in the placebo arm and were related to subject's decision (17.5%) and investigator's decision (7.5%).

Table 8 Subject Disposition—ITT Population

Category	Placebo N=40 n (%)	NPSP558 N=84 n (%)	Total N=124 n (%)
Completed treatment	33 (82.5)	79 (94)	112 (90.3)
Discontinued treatment early	7 (17.5)	5 (6)	12 (9.7)
Subject's decision	3 (17.5)	1 (1.2)	4 (3.2)
Lost to follow up	0	1 (1.2)	1 (0.8)
Adverse event	0	2 (2.4)	2 (1.6)
Investigator decision	3 (7.5)	0	3 (2.4)
Death	0	0	0
Other	1 (2.5)	1 (1.2)	2 (1.6)
Completed study/follow-up	32 (80)	79 (94)	111 (89.5)

From Applicant Submission dated May 27, 2014, Table B-14.1.1.5.1

In the NPSP558 group, 2 subjects discontinued due to adverse events. They are discussed in the Safety section of this review.

Protocol Violations and Compliance

Overall, approximately 14% of subjects had at least one protocol violation (protocol violations were pre-specified). They were included in the ITT population but excluded from the PP population. Most violations were related to compliance issues and occurred twice as often in the placebo arm.

Table 9 Summary of Significant Protocol Violations by Categories—All Randomized Subjects

Significant Protocol Violation	Placebo N=40 n (%)	NPSP558 N=84 n (%)	Total N=124 n (%)
Have at least 1 significant protocol violation	7 (17.5)	11 (13.1)	18 (14.5)
Study drug compliance outside of 80-120% range	7 (17.5)	7 (8.3)	14 (11.3)
No Week 24 efficacy determinations	7 (17.5)	5 (6)	12 (9.7)
Use of prohibited medications during the treatment period	0	1 (1.2)	1 (0.8)
Received wrong treatment kit	0	1 (1.2)	1 (0.8)
Key inclusion/exclusion criteria violation	0	1 (1.2)	1 (0.8)
Other	0	2 (2.4)	2 (1.6)

From Applicant Submission dated May 27, 2014, Table B-14.1.1.4

Overall, there were 900 non-significant protocol deviations (NPSP558, 616; placebo, 284). The majority of these were out-of-window visits (33% of total deviations), procedure errors (missing labs, visits, etc., 18%), and study drug-related issues (lost/damaged supplies, non-compliance,

concomitant medication, etc., 21%). There were no major differences in the deviations between the two treatment groups and none were found which could have impacted the ITT analyses.

Compliance was assessed from subject diaries and is summarized below for the trial. Subjects were considered compliant if the calculated compliance was ≥80%. According to this metric, compliance was high in both groups.

Table 10 Summary of Treatment Compliance—Safety Population

Treatment Compliance	**Placebo (N=40) n (%)**	**NPSP558 (N=84) n (%)**
N	4	84
Mean (SD)	96.5 (10.1)	97.1 (6.9)
Median	99.4	99.4
Min, Max	42, 100	51, 100
≥80%	38 (95)	82 (97.6)
<80%	2 (5)	2 (2.4)

From Applicant's Submission dated May 28, 2014, Table B-14.3.8.1

C. Dosing

As shown in the table below, the majority of subjects (56%) were titrated to the 100 µg dose. In this trial, down-titration to 25 µg was not an option.

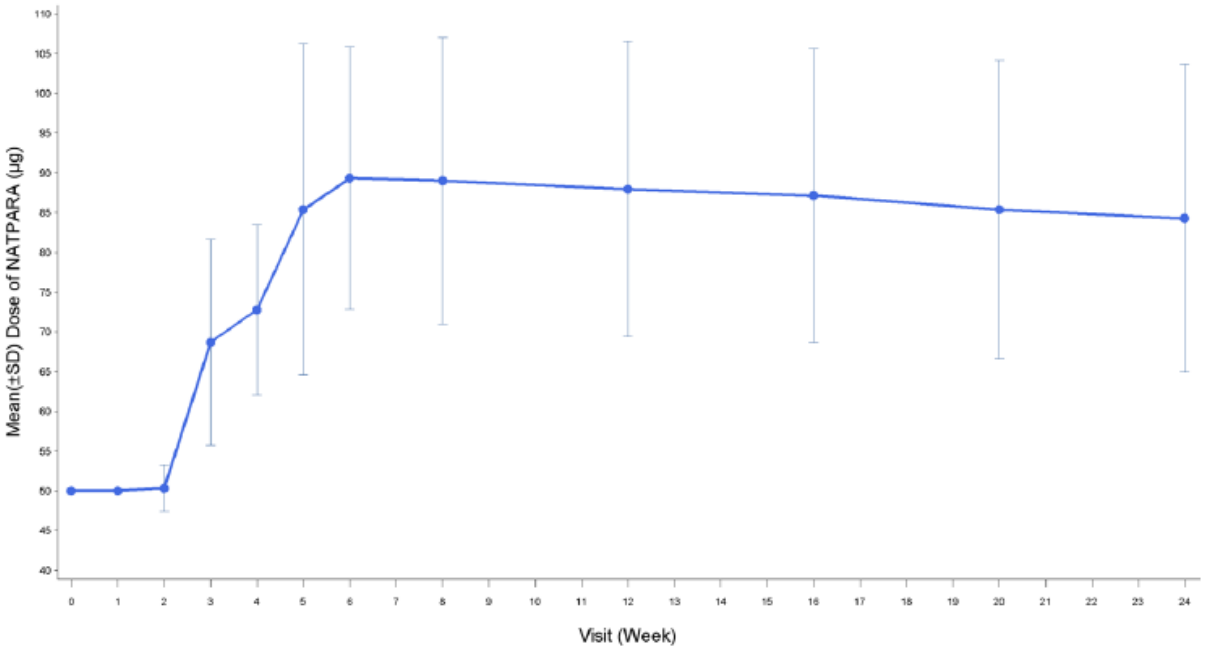
Table 11 Summary of Final NPSP558 Dose in the Pivotal Trial—ITT Population

Final NPSP558 Dose	**NPSP558 N=84 n (%)**
50 µg	15 (17.9)
75 µg	22 (26.2)
100 µg	47 (56)

From Applicant's Submission dated May 28, 2014, Table B-14.2.3.11

The figure below depicts the mean Natpara dose over time in the pivotal trial. The peak mean dose was reached at Week 6, and then declined minimally through Week 24.

Figure 3: Mean (±SD) Daily Dose of Natpara by Visit—ITT Population



From Applicant's Submission dated May 30, 2014, Figure 4b
Dose level at each visit is determined as the actual dose the subject received in or immediately prior to the day albumin-corrected serum calcium was tested for that visit.

D. Primary Efficacy Endpoint

In the pivotal trial, a subject was considered a responder at Week 24 if they safor the composite endpoint. Based on investigator-prescribed data, in the analysis below, approximately 55% of subjects in the NPSP558 group were responders compared to 2.5% in the placebo group. The results were statistically significant.

Table 12 Analysis of Responder Rate at End of Treatment Based on Investigator-prescribed Data—ITT Population

	Placebo N=40		NPSP558 N=84		Treatment Difference	
Status	**n (%)**	**(95% CI)**	**n (%)**	**(95% CI)**	**(95% CI)[a]**	**p-value[b]**
Responder	1 (2.5)	(0.1, 13.2)	46 (54.8)	(43.5, 65.7)	52.3 (40.6, 64)	<0.001
Non-Responder	39 (97.5)		38 (45.2)			

CI=confidence interval; ITT=intent-to-treat
[a] treatment difference is calculated as responder rate of NPSP558 minus the responder rate of placebo, the 2-sided asymptotic 95% CI is based on normal approximation
[b] based on Fisher's Exact test.
Applicant's Submission May 28, 2014, Table B-14.2.1.1.1

As previously discussed, Protocol Amendment 7 modified the definition of the third component of the primary endpoint. The Statistical Reviewer re-analyzed the data using a restricted reading of the original protocol definition, according to which serum calcium had to be in the 8-9 mg/dL range (rather than the whole normal range). Using this alternate definition, the number of responders dropped, but the efficacy results remain statistically significant. The results of the alternate analysis, however, may be more clinically relevant, particularly if a clinician's goal is to keep a patient's serum calcium in the lower half of the normal range.

Table 13 Alternate Analysis of Responder Rate at End of Treatment Using Serum Calcium Range of 8-9 mg/dL as Normal

Status	Placebo N=40		NPSP558 N=84		Treatment Difference (95% CI)	p-value[b]
	n (%)	(95% CI)	n (%)	(95% CI)		
Responder	1 (2.5)	(0.06, 13.16)	27 (32.1)	(22.36,43.22)	29.64 (18.55, 40.74)	<0.001
Non-Responder	39 (97.5)		57 (67.9)			

Analysis done by Dr. Jennifer Clark, FDA Statistician
CI=confidence interval

The primary efficacy analysis used investigator-prescribed data to approximate the actual dose that patients used. The Applicant conducted a sensitivity analysis using doses recorded by patients in subject diaries. The results of this analysis were consistent with the primary efficacy analysis.

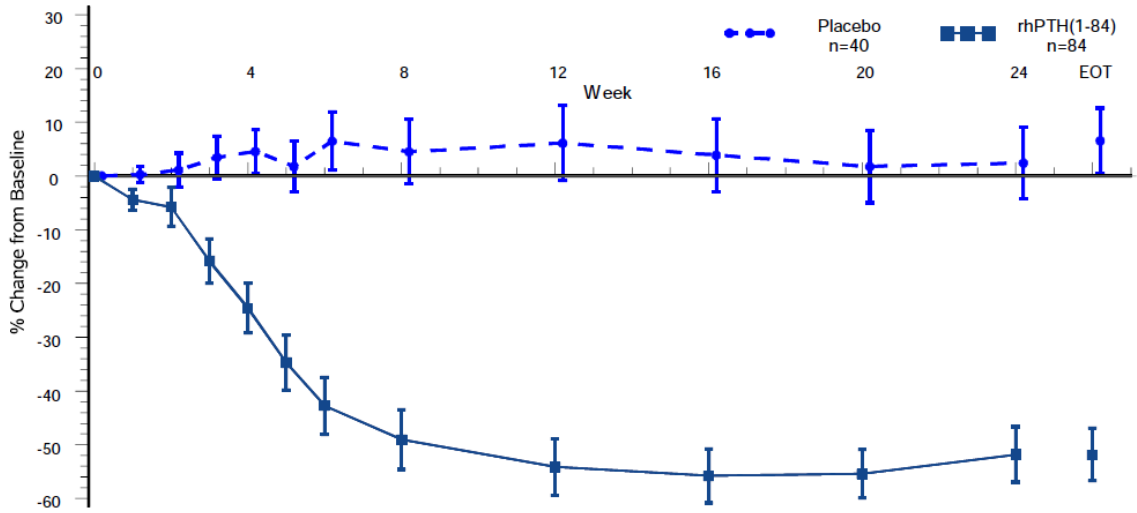
E. Secondary and Exploratory Efficacy Endpoints

The pivotal trial had a number of secondary and exploratory endpoints, which are presented next.

Percentage Change from Baseline in Daily Calcium Dose at Week 24

The figure below depicts the results of this endpoint. At Week 24, there was a mean percent decrease of 51.8% (±45.7%) in the NPSP558 group, compared to a minimal change in the placebo group (mean increase of 2.4% ±38.5%). This result is consistent with the dose-sparing effect regarding calcium supplementation demonstrated by the primary efficacy analysis.

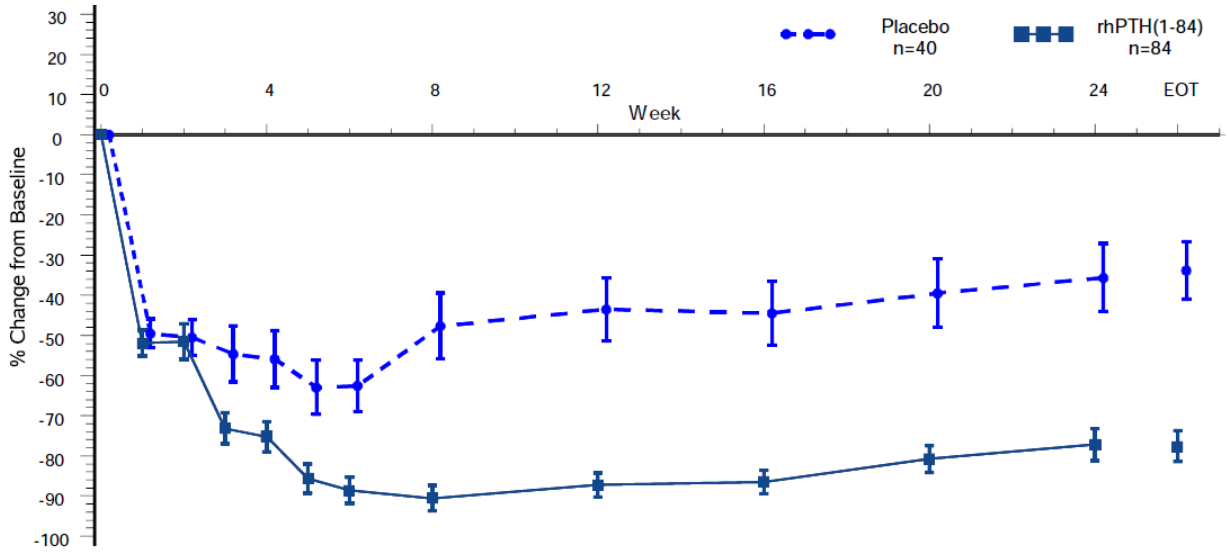
Figure 4: Mean (±SE).Percent Change from Baseline in Calcium Supplementation Dose Based on Investigator-prescribed Data-ITT Population



Applicant Submission dated May 28, 2014, Figure B-14.2.2.1.1

Although not a secondary endpoint, presented below is the percent change from baseline in active vitamin D/Vitamin D analog dose. This graph is displayed here in order to aid in understanding the changes of all three components of the primary endpoint during the REPLACE trial. In the Natpara arm there was a large percent decrease in the use of active vitamin D/Vitamin D analog during the titration period, which remained stable during the maintenance phase. A similar but lower percent decline occurred in the placebo group during active titration; a trend toward return to baseline levels was observed during the maintenance period, but even at the end of the trial the active Vitamin D/Vitamin D analog dose was reduced by about 1/3.

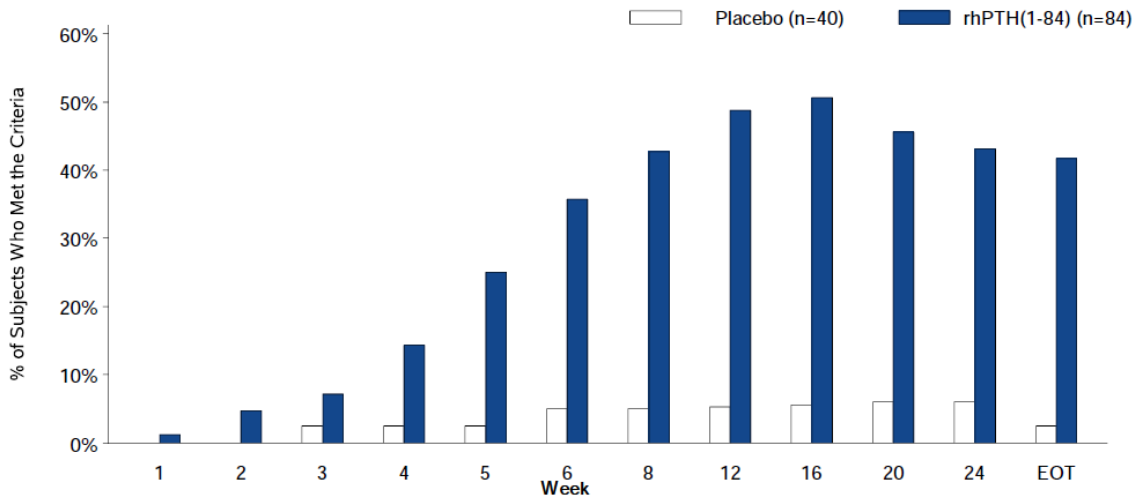
Figure 5: Mean (±SE) of Percent Change from Baseline in Active Vitamin D/Vitamin D Analog Dose Based on Investigator-prescribed Data-ITT Population



Proportion of Subjects Who Achieved Independence from Supplemental Active Vitamin D/Vitamin D Analog Usage and a Calcium Supplementation Dose of ≤500 mg/day

This secondary endpoint was intended to reflect the maximum feasible independence from oral supplements for hypoparathyroidism. This is reflected in the figure below, based on Investigator-prescribed data. By Week 24, a total of 36/84 (43%) of NPSP558-treated subjects achieved this goal, compared to only 2/40 (5.4%) of the placebo group.

Figure 6: Proportion of Subjects Who Achieved Independence from Supplemental Active Vitamin D /Vitamin D Analog Usage and a Calcium Supplementation Dose ≤500 mg/day Based on Investigator-Prescribed Data—ITT Population



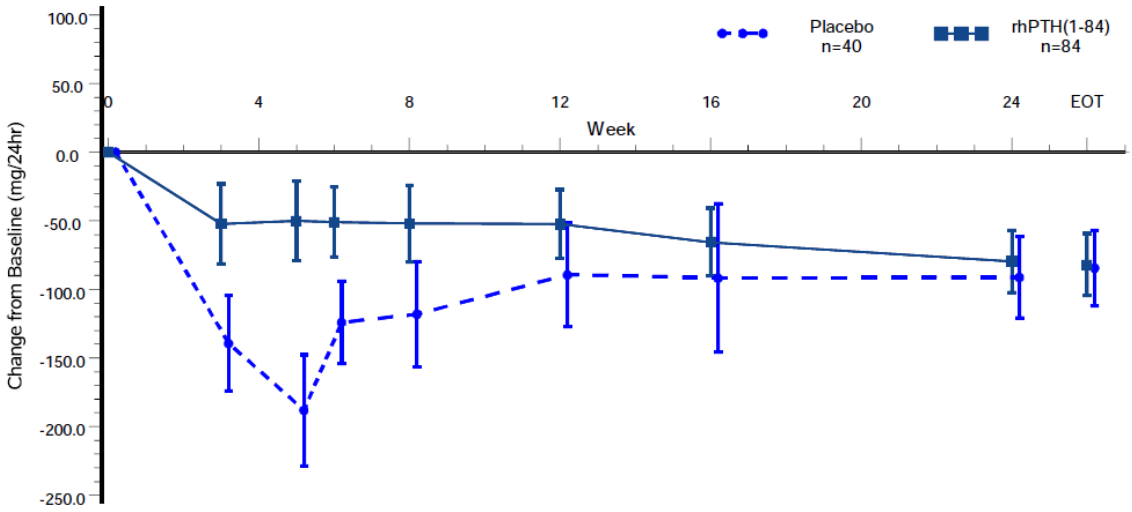
Applicant Submission dated May 28, 2014, Figure B-14.2.1.2.1

Several exploratory endpoints are discussed in this review because they measure effects of NPSP558 beyond sparing calcium and active Vitamin D/Vitamin D analog doses. For instance, when replacing parathyroid hormone, one would expect an improvement and/or reversal of the hypercalciuria that is observed in patients with the disease. Also, given that hypoparathyroidism is a low bone turnover state, one would predict positive changes in bone markers.

Change from baseline in 24-hour urine calcium excretion at Week 24

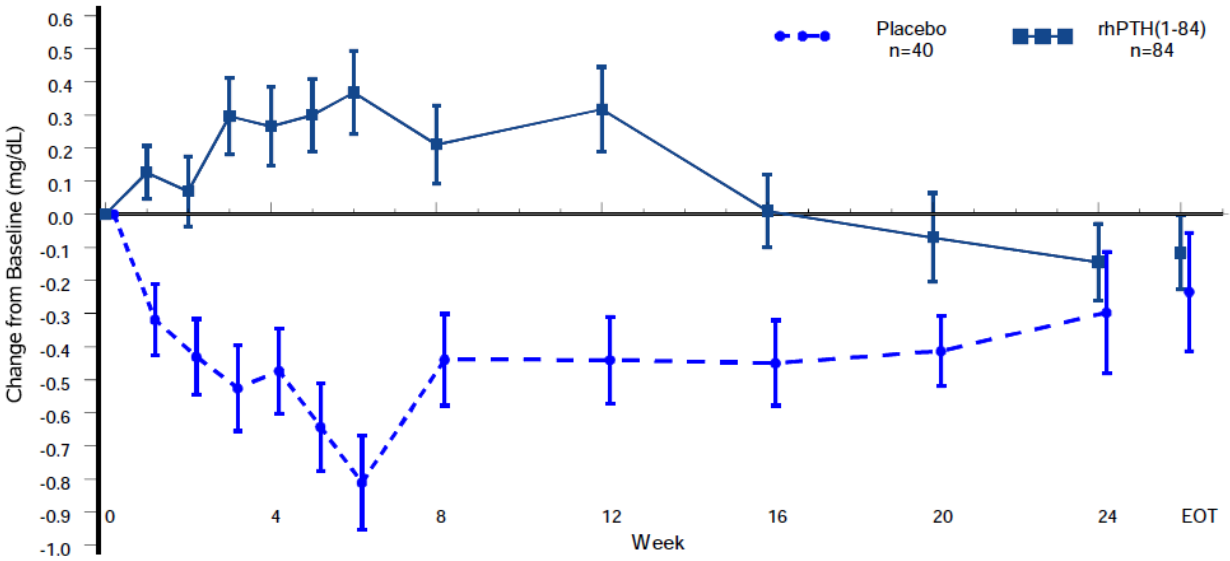
Hypoparathyroidism causes hypercalciuria and this complication results in morbidity, specifically, kidney stones, nephrocalcinosis and renal impairment. The figures below depict the mean change from baseline in 24-hour urinary calcium observed in REPLACE. Figure 7, below, shows that there were decreases in mean urinary calcium excretion in both groups (subsequent figures indicate that these changes largely paralleled changes in serum calcium). The placebo group had a steeper decrease in the first 8-12 weeks, reflecting reduction in calcium absorption due to the 50% reduction of the active vitamin D/Vitamin D analog dose. Since urinary calcium excretion and serum calcium levels are directly correlated average serum calcium levels are shown independently for the two groups (Figure 8) or overlaid with urinary calcium values in for each respective group in the figures below (Figures 9 Natpara Group and Figure 10 Placebo Group).

Figure 7: Mean (±SE) of Change from Baseline in 24-Hour Urinary Calcium Excretion –ITT Population



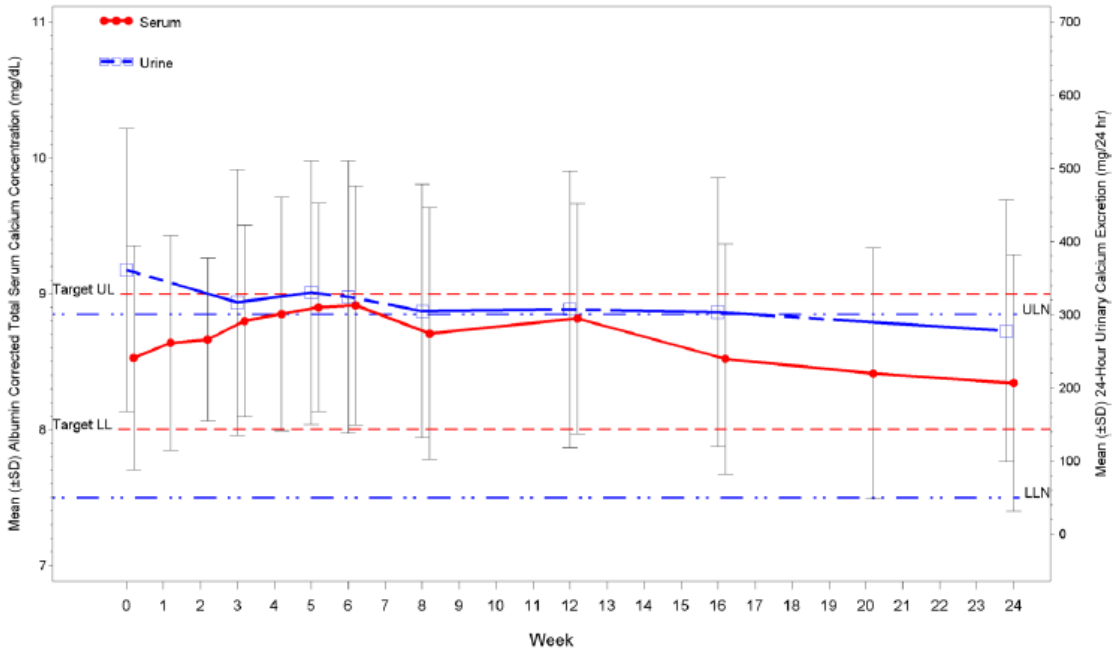
From Applicant's Submission dated May 28, 2014, Figure C-14.2.4.2

Figure 8: Mean (±SE) Change from Baseline in Albumin-corrected Total Serum Calcium—ITT Population, Excluding Site 1002



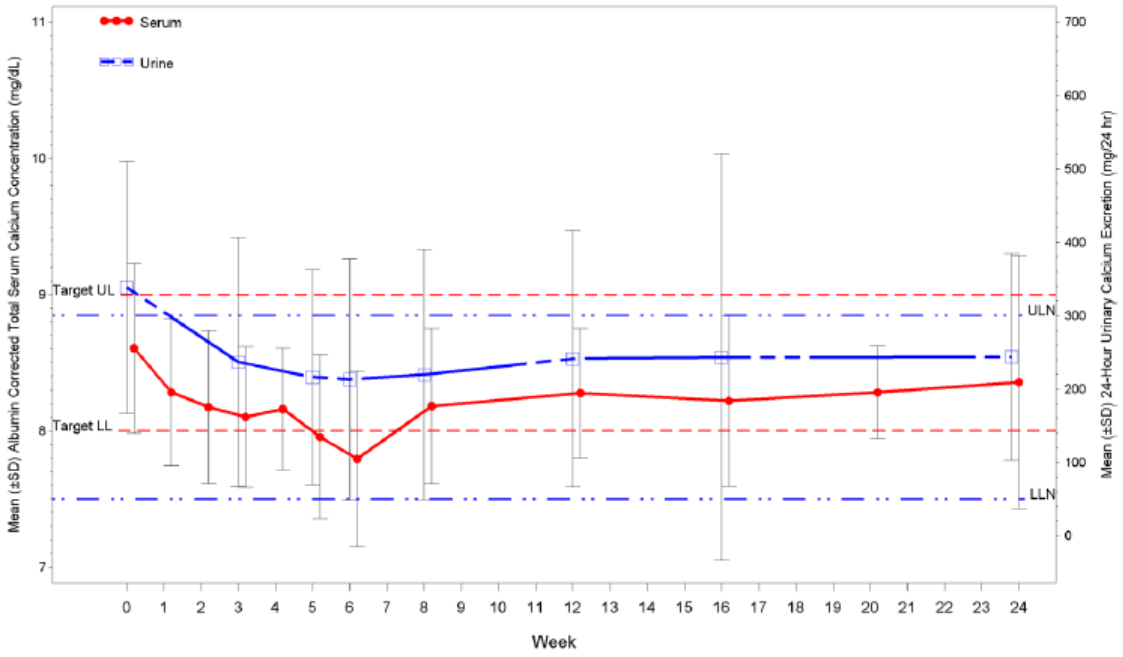
The two figures below show a similar pattern of changes for serum calcium and urinary calcium, the first for Natpara and the second for the placebo group. In both treatment groups the mean urinary calcium was within the normal range. The standard deviation, however, indicated large variability relative to the mean values.

Figure 9: Mean (±SD) Albumin-corrected Total Serum Calcium and Mean (±SD) 24-Hour Urinary Calcium Excretion—Natpara Group



From Applicant's Submission dated May 28, 2014, Figure C-14.2.4.2

Figure 10: Mean (±SD) Albumin-corrected Total Serum Calcium and Mean (±SD) 24-Hour Urinary Calcium Excretion—Placebo Group



Applicant's Submission dated June 11, 2014, Figure 4.2

The table below summarizes the 24 hour urine calcium data. The mean and median values and comparisons in 95% CI indicate that there were no real differences between the two treatment arms.

Table 14 Analysis of Change from Baseline in 24-Hour Urine Calcium Excretion at Week 24—ITT Population

	Placebo N=40		**NPSP558 N=84**	
Visit	Actual Value (mg/24 hr)	Change from Baseline (mg/24 hr)	Actual Value (mg/24 hr)	Change from Baseline (mg/24 hr)
Baseline				
n	40		84	
Mean (SD)	339 (172)		361 (193)	
Median	306		339	
Min, Max	49, 770		26, 973	
Week 24				
n	33	33	74	74
Mean (SD)	244 (141)	-91 (171)	276 (178)	-79 (194)
Median	232	-94	231	-78.5
Min, Max	32, 612	-431, 247	26, 915	-677, 432
LS Mean (SE)[a]		-100 (26)		-75 (17)

95% CI[a]		(-151, -48)		(-110, -40)
EOT				
n	39	39	84	84
Mean (SD)	252 (160)	-85 (171)	279 (175)	-82 (207)
Median	232	-59	244	-79
Min, Max	32, 761	-431, 247	26, 915	-677, 432
LS Mean (SE)[a]		-95 (25)		-77 (17)
95% CI[a]		-144, -45		-111, -43

EOT=End of Treatment

[a]= Based on ANCOVA model with actual change as the dependent variable and the treatment as the factor and baseline 24-hour urine calcium excretion as the covariate.

From Applicant's Submission dated May 28, 2014, Table B-14.2.3.2

The percentage of subjects in each group with normal or abnormal 24-hour urine calcium values is summarized below by visit. Please note that there were only two time points during the maintenance period: Week 16 and Week 24 (both highlighted in the table). At baseline, over 50% of subjects in each treatment group had abnormal urine calcium levels. During titration, the percentage of subjects with abnormal urine calcium decreased slightly in the rhPTH group. In contrast, there were greater decreases in the percentage of subjects with abnormal values in the placebo group for the same period. The two time point in the table that reflect the maintenance period (Week 16 and Week 24) do not show consistent differences between the two treatment arms.

Table 15 Number (%) of Subjects with Normal or Abnormal Urine Calcium Values (mg/24 hr) by Visit—Safety Population

	Placebo N=40			**rhPTH(1-84) N=84**		
Visit	m	Normal (≤300) n (%)	Abnormal (>300) n (%)	m	Normal (≤300) n (%)	Abnormal (>300) n (%)
Baseline	40	19 (47.5)	21 (52.5)	84	36 (42.9)	48 (57.1)
Week 3 (Titration)	21	17 (81)	4 (19)	61	36 (59)	25 (41)
Week 5	21	18 (85.7)	3 (14.3)	58	25 (43.1)	33 (56.9)
Week 6	27	20 (74.1)	7 (25.9)	63	37 (58.7)	26 (41.3)
Week 8	38	27 (70.1)	11 (28.9)	80	41 (51.3)	39 (48.8)
Week 12	32	22 (68.8)	10 (31.3)	77	41 (53.2)	36 (46.8)
Week 16	33	23 (69.7)	10 (30.3)	72	38 (52.8)	34 (47.2)
Week 24	33	20 (60.6)	13 (39.4)	74	49 (66.2)	25 (33.8)

m=number of subjects with 24-hour urine calcium excretion tested at each visit. Color highlight: time points during the maintenance phase.

Additional analyses (primarily scatterplots) that compare individual urine calcium values between the two treatment arms are presented in the Appendix. The results are consistent

with the general observation that there were no significant differences between the placebo and Natpara arms on urine calcium.

Proportion of patients that maintain a calcium –phosphate product in the normal range of 35-55 mg^2/dL^2 at Week 24 in the NPSP558 treatment group vs. placebo

At baseline, no subjects in the placebo group and one subject in the Natpara group had an elevated calcium-phosphate product. At Week 24, no subjects in the Natpara group had an elevated calcium-phosphate product and one subject in the placebo group had an elevated product. Scatterplots included in the Appendix indicate that almost all patients had calcium – phosphate product values below the upper limit of the normal range.

Bone turnover markers and changes in bone mineral density

Because of low or absent PTH, bone turnover markers (bone specific alkaline phosphatase, serum carboxy-terminal collagen crosslinks, serum type 1 procollagen, and osteocalcin) were predictably low in both groups at baseline. Not unexpectedly, all markers increased in the Natpara group but did not change in the placebo group at Week 24.

These changes associated with Natpara cannot be correlated, however, with any distinct clinical benefit since changes in bone mineral density (BMD) as measured by DXA were relatively small and inconsistent. Whether this is due to the short duration of the trial (clinically significant BMD changes take in general time to detect), or the dose regimen evaluated in the trial it remains to be determined.

DXA was measured at baseline and Week 24. Seven locations were scanned. Looking at Z-scores, statistically significant small changes from baseline were seen for total hip and hi—trochanter in the Natpara group compared to placebo. Five other locations—lumbar spine, hip, Ward's triangle, and distal one-third radius-- did not show changes that were statistically significant.

A summary of the DXA data for the pivotal trial is in the Appendix.

F. Efficacy conclusions

- The REPLACE trial demonstrated a statistically significant Natpara-to-placebo difference in the number of subjects who reduced their supplements of calcium and active Vitamin D/Vitamin D analogs below the pre-specified threshold (50% reduction), while maintaining a stable serum calcium in the low normal range. Applying this protocol-specified definition, 54.8% of subjects treated with a Natpara regimen of 50 µg to 100

μg daily were responders, compared to only 2.5% in the placebo group ($p<0.001$). Several sensitivity analyses confirmed the primary analysis.

- Results of secondary efficacy analyses were consistent with those of the primary efficacy analysis. By Week 24, 43% of Natpara-treated subjects and only 5.4% in the placebo arm achieved independence from active Vitamin D or Vitamin D analogs while reducing the supplemental calcium to no more than 500 mg daily (equivalent to one standard over the counter calcium tablet). Calcium supplementation was reduced by 51.8% in the Natpara group, and changed minimally in the placebo group (2.4% increase).

- The evidence of benefit beyond the dose-sparing effect was limited to favorable changes in several bone biomarkers, but the clinical importance of these changes is unclear, as they were not accompanied by meaningful changes in BMD measured by DXA.

- There was no evidence of clinical benefit with Natpara over placebo (standard of care) regarding reduction in urinary calcium. Changes in mean urine calcium profiles followed closely the changes in serum calcium which, in turn, changed in accordance to different titration decisions made in the Natpara and placebo groups. There were no real differences in mean changes from baseline to end-of-trial between treatment groups At Weeks 16 and 24, the only time points that measured urine calcium on maintenance regimens, the proportion of patients with hypercalciuria were largely similar between treatment arms.

- Whether the lack of benefit beyond dose-sparing is a consequence of the dose and/or dose regimen selection or the short duration of the trial (only 12 weeks of maintenance therapy) is not known.

IV. Supportive Efficacy Data

Although neither Trial 007 nor Trial 008 was placebo-controlled, these trials offer additional efficacy data that inform about Natpara dosing (Trial 007) and potential for durability of treatment (Trial 008). In this section, these trials are briefly described and primary efficacy results presented. A more complete review of each trial can be found in the Appendix.

A. Trial 007

Following the pivotal trial, in which the lowest dose was 50 µg, the Applicant decided to conduct a trial looking at the lower 25 µg dose. Trial 007 was a randomized, dose-blinded, fixed-dose trial. Hypoparathyroid subjects, who were required to have completed the pivotal trial or a Clinical Pharmacology study, were randomized to receive either Natpara 25 µg or Natpara 50 µg in a fixed-dose fashion. This 8-week trial had 4 scheduled study visits.

The primary efficacy endpoint was slightly different than that of the pivotal trial. Specifically, a subject was considered a responder if they met the following 3 criteria at Week 8:

• A reduction in oral calcium supplementation to ≤ 500 mg/day and

• A reduction in calcitriol dose to ≤ 0.25 µg/day and

• An albumin-corrected total serum calcium level between 7.5 mg/dL and the upper limit of normal (ULN) for the central laboratory

This trial enrolled a total of 42 subjects. The primary response rate, summarized below, was based on investigator-prescribed data. Only 21% of subjects in the 25 µg group were considered responders compared to 26% of the 50 µg group. It should be noted that if patient diary data was used, only one subject in each group met the primary endpoint.

Table 16 Primary Response Rate at Week 8 Based on Investigator-prescribed Data—ITT Population

	rhPTH (1-84) 25 µg N=19		**rhPTH (1-84) 50 µg N=23**			
Status	n (%)	(95% CI)	n (%)	(95% CI)	Treatment Difference (95% CI)	p-value
Responder Non-responder	4 (21.1) 15 (78.9)	(6.1, 45.6)	6 (26.1) 17 (73.9)	(10.2, 48.4)	5.0 (-20.6, 30.7)	>0.999

From Applicant's Submission dated June 5, 2014, Table B-14.2.1.1.1

Percentages are based on the number of ITT subjects in each treatment arm. Responder is defined as subjects whose daily calcium supplementation at Week 8 was ≤500 mg/day and the daily calcitriol dose was ≤0.25 µg/day and the

albumin-corrected calcium level at Week 8 was between 7.5 mg/dL and the upper limit of normal. Subjects who terminated early or had missing lab data at Week 8 were considered non-responders.

This trial is discussed in detail in the Appendix.

B. Trial 008

This is an ongoing, long-term (52 weeks plus extension period), open-label trial in adults with hypoparathyroidism. Importantly, there is no control group. The majority of subjects enrolled in this trial either completed the pivotal trial or Trial 007. Subjects enrolled in previous trials had undergone a washout of Natpara prior to enrollment in Trial 008. The purpose of the trial was to assess the long-term safety and tolerability of Natpara. In this trial supplemental calcitriol and oral calcium were down-titrated to as low as safely possible based total serum calcium levels. The starting doses were 25 or 50 μg, depending on an algorithm.

At any time during this trial, the dose of NPSP558 could be increased in increments of 25 μg to a maximum of 100 μg, with the goal of achieving or maintaining total serum calcium levels in the range of 8-9 mg/dL. The dose could be down-titrated at any time for efficacy or safety reasons.

At the end of Week 52, subjects were invited to enter a second year extension period. During this time, subjects were to return to the clinic every 2 months.

The primary efficacy endpoint again was slightly different than that of the pivotal trial. Specifically, a subject was considered a responder if he/she met the following criteria at Week 52 and at the End of Treatment (EOT):

- A ≥50% reduction from baseline in dose of oral calcium supplementation or an oral calcium dose of ≤500 mg
  AND
- A ≥50% reduction from baseline in dose of oral calcitriol supplementation or an oral calcitriol dose of ≤0.25 μg
  AND
- An albumin-corrected total serum calcium concentration that is normalized or maintained compared to the baseline value (≥7.5 mg/dL) and does not exceed the ULN of the central laboratory

The analysis of responder rate is summarized below. The reasons for the difference between the Week 52 and EOT analyses is unclear.

Table 17 Analysis of Responder Rate Based on Investigator-prescribed Data

	NPSP558 (N=49)	
	n/m (%)	(95% CI)
Week 52		
Responder	34/45 (75.6)	(60.5, 87.1)
Non-responder	11/45 (24.4)	
End of Treatment		
Responder	25/48 (52.1)	(37.2, 66.7)
Non-responder	23/48 (47.9)	

Percentages are based on 'm', the number of ITT subjects with valid responder values available at the visit.

From Applicant's Submission dated June 2, 2014, Table B-14.2.1.1.1

In Trial 008, change in 24 hour urinary calcium was a secondary endpoint. At baseline (n=52), the mean (±SD) 24-hour urinary calcium excretion was 354.33 (±196.96) mg/24 hr. At Week 52 (n=48), the mean 24-hour urinary calcium excretion was 317.31 (±174) mg/24 hr.

Finally, the DXA data for the pivotal trial was limited because of the limited duration of treatment. Trial 008 offered an opportunity to observe changes with more a more extended treatment period. Measurements were done at baseline and at Week 52. Changes at Week 52 were minimal.

VI. Safety Results in Trial CL1-11-040 (REPLACE)

A. Exposure

Mean exposure to study drug in the pivotal trial was 168 days. There were no major differences in duration of treatment between the placebo and the NPS558 arm.

Table 18 Summary of Exposure in Trial 040—Safety Population

Extent of Exposure	**Placebo N=40 n (%)**	**NPSP558 N=84 n (%)**
Any exposure	40 (100)	84 (100)
< 1 week	0	0
1 to < 4 weeks	0	0
4 to < 8 weeks	1 (2.5)	2 (2.4)
8 to < 12 weeks	2 (5)	0
12 to < 16 weeks	3 (7.5)	2 (2.4)
16 to < 20 weeks	1 (2.5)	1 (1.2)
20 to < 24 weeks	2 (5)	10 (11.9)
≥ 24 weeks	31 (77.5)	69 (82.1)
Exposure duration (days)		

Mean (SD)	157.3 (34.5)	168 (25.9)
Median	169	170
Min, Max	48, 185	40, 213

From Applicant's Submission Dated May 28, 2014, Table B-14.3.8.2

B. Adverse Events

The table below summarizes adverse event (AE) incidence by general categories. There were no deaths in the clinical trial. Two subjects in the NPSP558 group had an AE leading to discontinuation. After reviewing the subject narratives, the discontinuations do not appear to be related to study drug. Similar percentages of subjects experienced serious adverse events[6] (10% and 10.7%, respectively for placebo and NPSP558).

Table 19 Summary of Adverse Events—Safety Population

	Placebo		**NPSP558**	
Category	**Subjects N=40 n (%)**	**Events**	**Subjects N=84 n (%)**	**Events**
Any AE				
No	0		6 (7.1)	
Yes	40 (100)	321	78 (92.9)	807
AE leading to discontinuation	0	0	2 (2.4)	14
Any SAE	4 (10)	5	9 (10.7)	11
Deaths	0	0	0	0

From Applicant's Submission dated May 28, 2014, Table B-14.3.1.1.1

Brief narratives for the two discontinuations are provided below:

1) One subject who had a history of hypertension and a previous 24-year history of smoking discontinued on Day 122 after experiencing a cerebrovascular accident (also recorded as an SAE).
2) A second subject withdrew on Day 58 due to multiple non-serious adverse events, including anxiety, depression, injection site erythema, nausea as well as an event of hypercalcemia (11 mg/dL) one day following Natpara discontinuation, which was described as resolved.

[6] A serious adverse event is an AE that results in any of the following outcomes: death, is life-threatening, results in persistent or significant incapacity with substantial disruption of ability to conduct normal life functions, results in hospitalization or prolongation of existing hospitalization, or results in a congenital anomaly/birth defect.

The listing of serious adverse events (SAEs) in the REPLACE trial is included in the table below. Of all the SAEs observed during Natpara treatment, only one (hypercalcemia) appeared to be related to study drug. Narratives for the other SAEs were reviewed and had plausible alternative explanations that did not implicate Natpara as a cause.

All 3 SAEs of hypocalcemia occurred during the follow-up period, after Natpara treatment drug was discontinued, as calcium and active Vitamin D/Vitamin D analog supplements were restarted.

Table 20 Summary of Serious Adverse Events by System Organ Class (SOC) and Preferred Term (PT) During the Entire Trial (Treatment plus Observation)—Safety Population

	Placebo		NPSP558	
MedDRA SOC PT	Subjects N=40 n (%)	Events	Subjects N=84 n (%)	Events
Any SAE				
No	36 (90)		75 (89.3)	
Yes	4 (10)	5	9 (10.7)	11
Metabolism and Nutrition Disorders	2 (5)	2	4 (4.8)	4
Hypocalcemia	1 (2.5)	1	2 (2.4)	2
Hypercalcemia	0	0	2 (2.4)	2
Dehydration	1 (2.5)	1	0	0
Gastrointestinal Disorder	0	0	2 (2.4)	3
Diarrhea	0	0	1 (1.2)	1
Pancreatitis	0	0	1 (1.2)	1
Vomiting	0	0	1 (1.2)	1
Infections and Infestations	0	0	2 (2.4)	2
Diverticulitis	0	0	1 (1.2)	1
Erysipelas	0	0	1 (1.2)	1
Musculoskeletal and Connective Tissue Disorder	0	0	1 (1.2)	1
Back pain	0	0	1 (1.2)	1
Nervous System Disorders	0	0	1 (1.2)	1
Cerebrovascular accident	0	0	1 (1.2)	1
Reproductive system and breast disorders	1 (2.5)	1	0	0
Epididymal tenderness	1 (2.5)	1	0	0
Respiratory, thoracic and mediastinal disorders	1 (2.5)	1	0	0
Asthma	1 (2.5)	1	0	0
COPD	1 (2.5)	1	0	0

Applicant's Submission dated May 28, 2014, Table B-14.3.2.3.1

Treatment-emergent adverse events occurred with similar frequencies in the NPSP558 (76%) and the placebo arm (85%). Of note, there is a small imbalance in hypocalcemia incidence (20%

placebo, 25% study drug), and a larger one for hypercalcemia (2.5% placebo and 16.7% study drug). Both hypocalcemia and hypercalcemia are discussed in detail in the next section of this review. Vomiting and diarrhea clearly occurred with higher frequency in the NPSP558 arm but there is no biological basis for this association. Other adverse event imbalances were minor and of no apparent consequence.

Table 21 Summary of Adverse Events in >4% and greater in NPSP558 group compared to placebo, during the treatment period, in decreasing order of frequency—Safety Population

	Placebo		**NPSP558**	
Preferred Term	**Subjects N=40 n (%)**	**Events**	**Subjects N=84 n (%)**	**Events**
Any TEAE>4%				
No	6 (15)		20 (23.8)	
Yes	34 (85)	142	64 (76.2)	438
Paresthesia	10 (25)	14	26 (31)	54
Headache	9 (22.5)	17	21 (25)	53
Hypocalcemia	8 (20)	8	21 (25)	34
Nausea	7 (17.5)	8	15 (17.9)	33
Hypercalcemia	1 (2.5)	1	14 (16.7)	17
Hypoesthesia	4 (10)	5	12 (14.3)	18
Diarrhea	1 (2.5)	1	10 (11.9)	13
Vomiting	0	0	10 (11.9)	12
Arthralgia	4 (10)	4	9 (10.7)	16
Pain in Extremity	3 (7.5)	3	8 (9.5)	11
URI	2 (5)	2	7 (8.3)	7
Sinusitis	2 (5)	2	6 (7.1)	6
Hypercalciuria	1 (2.5)	1	6 (7.1)	7
Neck Pain	1 (2.5)	1	5 (6)	5
Hypertension	2 (5)	2	5 (6)	5
Blood 25-Hydroxycholecalciferol decreased	1 (2.5)	1	5 (6)	5
Facial Hypoesthesia	1 (2.5)	1	5 (6)	5
Peripheral Edema	1 (2.5)	1	4 (4.8)	4
Thirst	0	0	4 (4.8)	5
Anxiety	0	0	4 (4.8)	4

From Applicant's Response to Information Request dated June 23, 2014

Treatment period defined as from the first dose date to the last dose date.

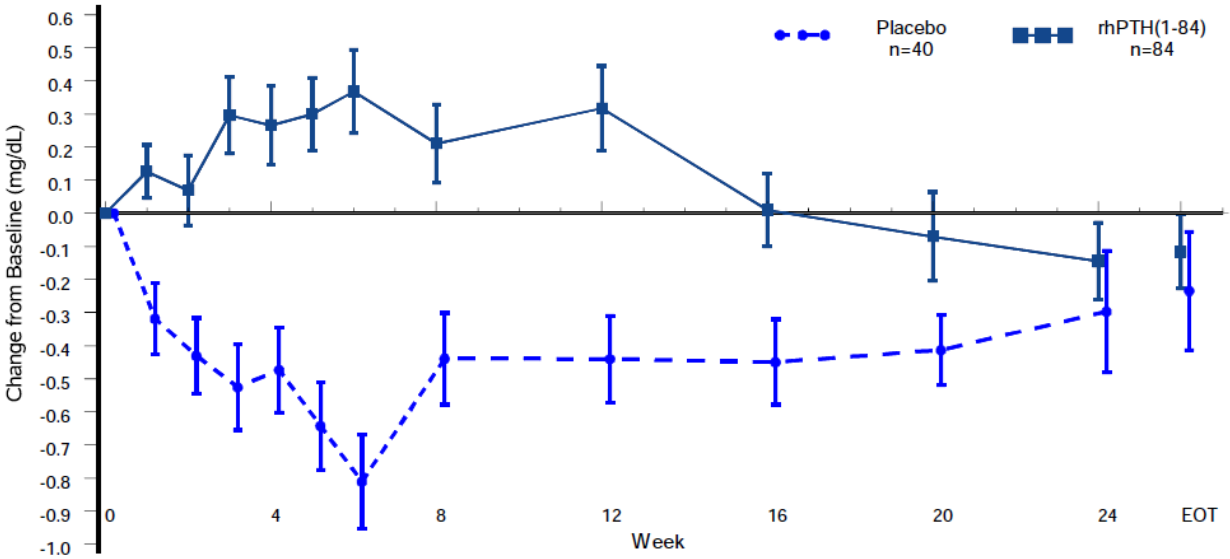
GERD=gastroesophageal reflux disease

URI=urinary tract infection

C. Analyses of Hypocalcemia and Hypercalcemia

Hypocalcemia and hypercalcemia must be understood in the context of drug titration. The REPLACE protocol included guidelines for investigators to maintain subjects' total serum calcium in the range of 8 to 9 mg/dL. The figure below depicts the mean change from baseline in serum calcium over 24 weeks. The serum calcium over time differed somewhat between the two treatment arms but not considerably (changes from baseline did not exceed 0.8 mg). The differences in serum calcium profile are a direct consequence of the protocol-mandated adjustments in rhPTH, active Vitamin D/Vitamin D analog supplement, and oral calcium. As one would predict, with the immediate 50% reduction in active vitamin D/Vitamin D analog and concomitant introduction of study drug, the placebo group had an initial decrease in serum calcium. On the other hand, there was an initial trend toward higher serum calcium values in the NPSP558 group. During the maintenance period, mean serum calcium in the two treatment arms gradually converged.

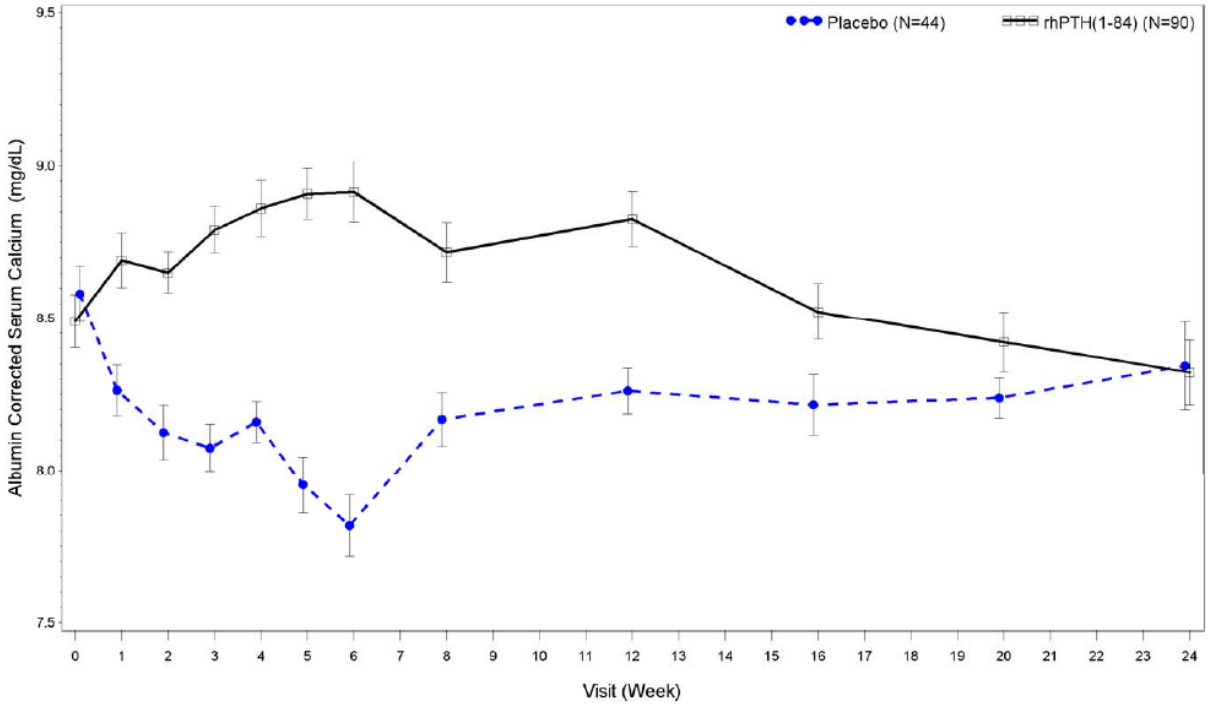
Figure 3 Mean (±SE) Change from Baseline in Albumin-corrected Total Serum Calcium—ITT Population



Applicant's Submission dated May 28, 2014, Figure B-14.2.4.1

The following figure depicts the actual mean values (rather than mean change) over time. In general, mean serum calcium values remained within the goal of 8.0 to 9.0 mg/dL.

Figure 4 Mean (±SE) Albumin-corrected Total Serum Calcium –ITT Population



Applicant's Response to Information Request, January 24, 2014

Descriptive statistics of serum calcium at baseline, Week 24, and end-of-trial (EOT) are summarized below. Refer to the Appendix for a table with serum calcium values at all intermediate time points.

Table 22 Analysis of Albumin-corrected Total Serum calcium Concentration (mg/dL) —ITT Population

	Placebo N=40	**NPSP558 N=84**
Baseline		
n	40	84
Mean (SD)	8.6 (0.6)	8.5 (0.8)
Median	8.6	8.5
Min, Max	7.2, 9.8	5.2, 11.3
Week 24		
n	33	78
Mean (SD)	8.4 (0.9)	8.3 (0.9)
Median	8.3	8.3
Min, Max	7.4, 12.7	5.5, 11.5
EOT		

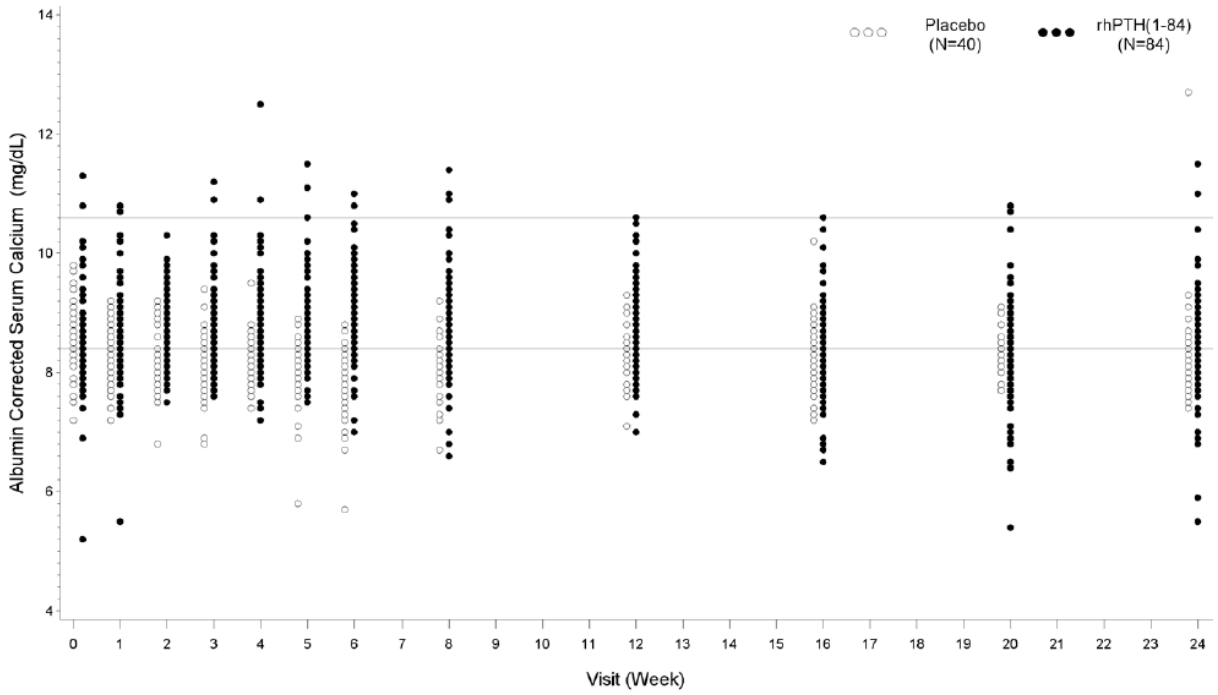
n	40	84
Mean (SD)	8.4 (0.9)	8.4 (0.9)
Median	8.3	8.3
Min, Max	7.1, 12.7	6.8, 11.5

From Applicant's Submission dated May 28, 2014, Table B-14.2.3.8
Normal albumin-corrected total serum calcium concentration for the trial were 8.4-10.6 mg/dl.

Beyond understanding the mean changes in serum calcium levels, it is equally important to understand the distribution of serum calcium levels observed in treated subjects. The figure below is a scatterplot of all serum calcium data points for the noted study visits for both groups. The two shaded horizontal lines represent the upper and lower limits of normal for serum calcium.

These data should be interpreted in the context of titration (see analyses of hypocalcemia and hypercalcemia below). Also, it is important to recognize that although patients were randomized and the mean calcium levels at baseline were similar, the range was much wider in the Natpara group (5.2 to 11.5 mg/dl vs. 7.7 to 9.8 mg/dl in the placebo arm). Therefore, when looking at differences in percentages of subjects with hypercalcemia and hypocalcemia, one must consider both the active titration as well as the between-group individual patient differences at baseline. Of additional interest, in the Natpara group, the distribution of serum calcium was similar for Week 0 and Week 24.

Figure 5 Scatterplot of Albumin-corrected Serum Calcium (mg/dL) by Study Visit—ITT Population



From Applicant's Submission dated May 30, 2014, Figure 5b
ULN=10.6 mg/dL and lower limit of normal=8.4 mg/dL

The incidence of patients with biochemically defined hypercalcemia and hypocalcemia is summarized below by study period. One would expect more hyper- and hypocalcemia during the titration period when the active drug regimen and supplements were continually adjusted, and less during the maintenance period, when the two different regimens were stable.

During the titration period, no placebo subjects developed calcium levels in the hypercalcemic range (>10.6 mg/dl). This observation is consistent with the calcium and active Vitamin D/Vitamin D analog reductions implemented in this arm. In contrast, as many as 31% of subjects in the Natpara group developed hypercalcemia. The higher incidence of hypercalcemia in the Natpara group during titration phase may indicate that Natpara titration could be initiated at doses below 50 µg (or that calcium and Vitamin D reduction may need to be pursued more aggressively with the 50 µg dose). The noted imbalance of subjects' baseline serum calcium may contribute as well to the extent to which they are indicators of different ways in which these subjects may respond to the same titration scheme. Regardless, there were only 2 patients with serum calcium values > 12 mg/dl in the Natpara arm (and both were < 13 mg/dl).

During the maintenance period, hypercalcemia remained more frequent in in the Natpara group compared to placebo but the incidence during this period was markedly lower than during the titration period. It was also relatively mild and did not exceed levels of 12 mg/dl.

Table 23 Hypercalcemia Incidence—ITT Population

	Titration Period Weeks 0-12		**Maintenance Period Week 12-24**		**Trial Duration Weeks 0-24**	
Albumin-Corrected Serum Calcium	Placebo N=40 n (%)	rhPTH(1-84) N=84 n (%)	Placebo N=40 n (%)	rhPTH(1-84) N=84 n (%)	Placebo N=40 n (%)	rhPTH(1-84) N=84 n (%)
>10.6 mg/dL	0	26 (31)	1 (2.5)	8 (9.5)	1 (2.5)	31 (36.9)
>10.6 and ≤11 mg/dL	0	19 (22.6)	0	6 (7.1)	0	23 (27.4)
>11 and ≤12 mg/dL	0	11 (13.1)	0	2 (2.4)	0	12 (14.3)
>12 and ≤13 mg/dL	0	2 (2.4)	1 (2.5)	0	1 (2.5)	2 (2.4)
>13 and ≤14 mg/dL	0	0	0	0	0	0
>14 mg/dL	0	0	0	0	0	0

From Applicant's Submission dated May 31, 2014, Table 5.1b
There are multiple scheduled lab tests for albumin-corrected serum calcium within each period. In each period, a subjects is counted only once at a given category, but could be counted at different categories.
Percentages are based on the total number of subjects in each treatment group. Baseline values are excluded from analysis.

As expected, the incidence of hypocalcemia was higher in the placebo group during the titration phase because of the reduction in active Vitamin D/Vitamin D analog, and subsequent effect on calcium absorption. There were no major differences between the two groups during the maintenance phase, although there appeared to be more patients treated with Natpara who experienced hypocalcemia of greater severity (such as below 7 mg/dl). To what extent this is due to differences in patient characteristics or the treatment itself remains to be determined.

Table 24 Hypocalcemia Incidence—ITT Population

	Titration Period Weeks 0-12		**Maintenance Period Week 12-24**		**Trial Duration Weeks 0-24**	
Albumin-Corrected Serum Calcium	Placebo N=40 n (%)	rhPTH(1-84) N=84 n (%)	Placebo N=40 n (%)	rhPTH(1-84) N=84 n (%)	Placebo N=40 n (%)	rhPTH(1-84) N=84 n (%)
<8.4 mg/dL	39 (97.5)	67 (79.8)	30 (75)	60 (71.4)	40 (100)	75 (89.3)
>8 and <8.4 mg/dL	35 (87.5)	55 (65.5)	22 (55)	34 (40.5)	37 (92.5)	64 (76.2)
>7 and ≤8 mg/dL	36 (90)	50 (59.5)	18 (45)	49 (58.3)	36 (90)	69 (82.1)
>6 and ≤7 mg/dL	8 (20)	7 (8.3)	1 (2.5)	10 (11.9)	9 (22.5)	14 (16.6)
>5 and ≤6 mg/dL	1 (2.5)	1 (1.2)	0	3 (3.6)	1 (2.5)	3 (3.6)

<5 mg/dL	0	0	0	0	0	0

From Applicant's Submission dated May 31, 2014, Table 5.2b

There are multiple scheduled lab tests for albumin-corrected serum calcium within each period. In each period, a subjects is counted only once at a given category, but could be counted at different categories.

Percentages are based on the total number of subjects in each treatment group. Baseline values are excluded from analysis.

D. Analyses of Change in Phosphorus

Serum phosphorus levels are increased in hypoparathyroidism. The table below summarizes phosphorus levels during the trial. In the Natpara group, mean levels decreased from 4.5 mg/dL to 4 mg/dL, while they remained virtually unchanged in the placebo group. Both Natpara and placebo mean values were within the normal range.

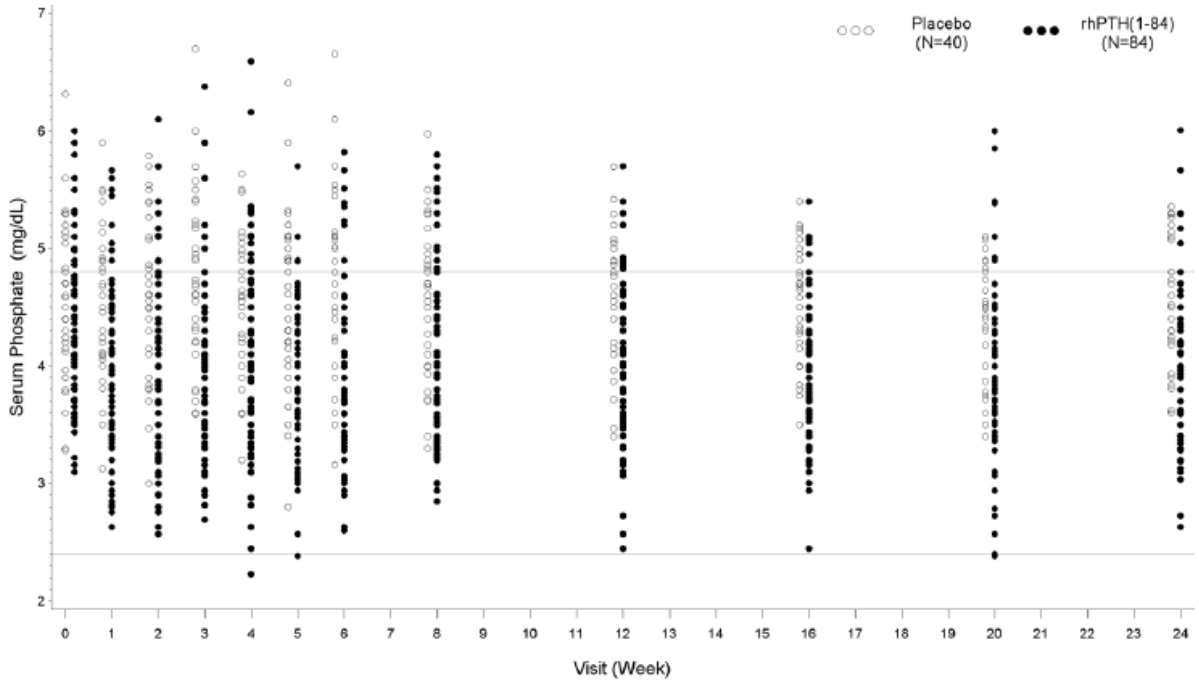
Table 25 Phosphorus levels at baseline and Week 24 in the pivotal trial—ITT Population

	Placebo N=40	**NPSP558 N=84**
Baseline		
n	40	84
Mean (SD)	4.5 (0.7)	4.5 (0.7)
Median	4.5	4.5
Min, Max	3.3, 6.3	3.1, 6
Week 24		
n	33	78
Mean (SD)	4.5 (0.5)	4 (0.7)
Median	4.5	4
Min, Max	3.6, 5.4	2.6, 6

ULN=4.8, LLN=2.4 mg/dL

The plot below represents all data points for phosphorus by trial visit. As expected, hyperphosphatemia was prevalent in both groups, particularly at baseline.

Figure 6 Scatterplot of Serum Phosphorus (mg/dL) by Study Visit—ITT Population



From Applicant's Submission dated May 30, 2014, Figure 6b

ULN=4.8, LLN=2.4

E. Safety Findings in Trials 007 and 008

Overall, the safety findings in these trials were consistent with those of the pivotal trial. In Trial 007, as expected, mean serum calcium levels in the 25 µg group were lower compared with the 50 µg group.

F. Immunogenicity

In the REPLACE trial (24 weeks duration), the incidence of anti-PTH antibodies was 8.8% (3/34) in the Natpara group and 5.9% (1/17) in the placebo arm. Across all NPS clinical studies conducted in patients with hypoparathyroidism, following treatment with Natpara for up to 2.6 years, the immunogenicity incidence rate was 16.1% (14 out of 87 patients developed antibodies). These 14 patients had low titer anti-PTH antibodies and 3 of them subsequently became antibody negative. Only one patient in the whole program had a positive neutralizing antibody assay. This patient, however, maintained a clinical response with no evidence of immune-related adverse reactions.

G. Safety Conclusions

- There were no deaths in any of the trials.
- In the pivotal trial, serious adverse events were observed at a similar frequency in both NPSP558- and placebo-treated subjects. Of the two SAEs of hypercalcemia recorded in the Naptara group, upon further review, only one appears to be drug-related.
- There was an imbalance in the incidence of treatment-emergent adverse events of hypocalcemia (20% placebo, vs. 25% Natpara), and hypercalcemia (2.5% placebo and 16.7% Natpara). These differences must be interpreted in the context of the background titration of study drug and supplements.
- Biochemically confirmed hypercalcemia was mostly seen during the titration period when the Natpara dose was initiated and up-titrated while calcium and active Vitamin D/Vitamin D analog supplements were gradually reduced. The incidence decreased during the maintenance period, as did the imbalance relative to the placebo arm.
- In contrast, the incidence of hypocalcemia was higher in the placebo group during the titration phase secondary to the reduction in active Vitamin D /Vitamin D analog and calcium supplements. There were no major differences between the two groups during the maintenance phase, although more patients treated with Natpara experienced hypocalcemia of greater severity below 7 mg/dl).
- Between-group differences in incidence or severity of hypercalcemia/hypocalcemia may not reflect only the use of Natpara and different titrations of supplemental calcium and Vitamin D/Vitamin D analogs in the two treatment groups. Between-group differences of patient characteristics may contribute as well.
- Overall, the incidence of anti-drug antibodies in the Natpara program was 16.1%. Within the limitations of the immunogenicity testing there was no evidence for loss of efficacy associated with antibodies and there were no adverse events that correlated with the presence of antibodies.
- In Trial 007 and 008, the safety profile of Natpara was consistent with that observed in the pivotal trial.

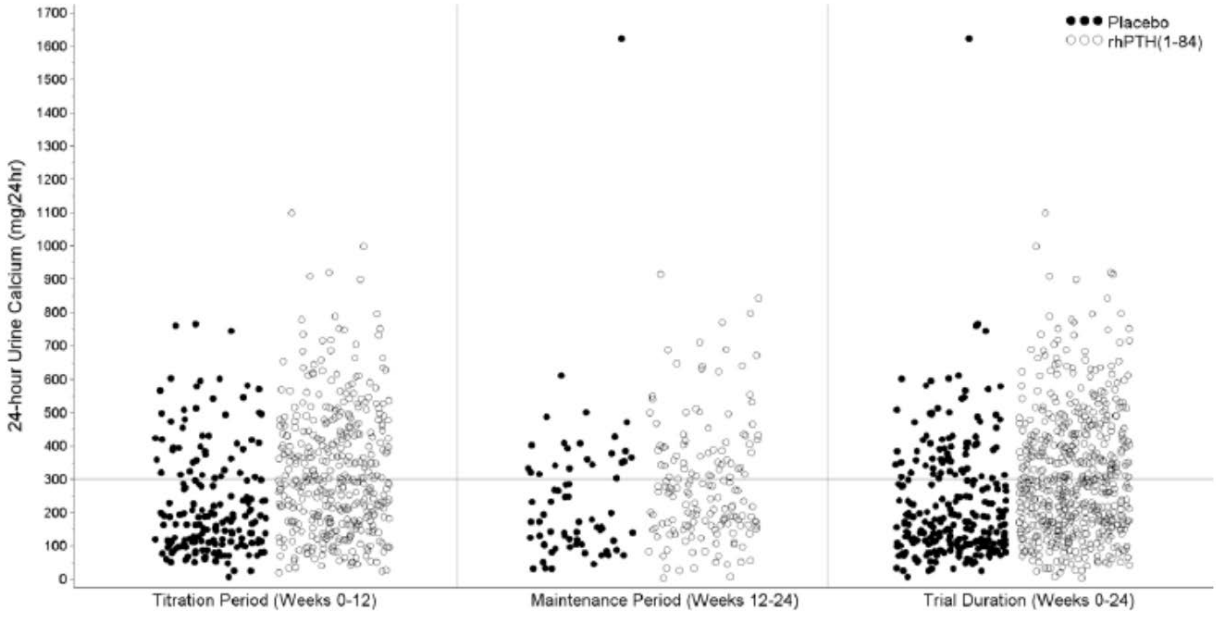
VIII. Appendices

A. Additional Analyses of Urine Calcium

In order to better understand the individual changes in 24-hour urine calcium, the Division asked the Applicant for several analyses. These are presented here.

The first graph below is a scatterplot showing the distribution of 24-hour urine calcium measurements. Not all study subjects had 24-hour urine collections. The total number of data points is described below the graph. The second graph is a scatterplot of all 24-hour urine calcium levels with serum calcium recorded on the same day. For both graphs the upper limit of normal value of 300 mg/dl is represented. Overall, hypercalciuria was problematic in both groups.

Figure 7 24-hour urine calcium (mg/24 hours) by Study Period—ITT Population

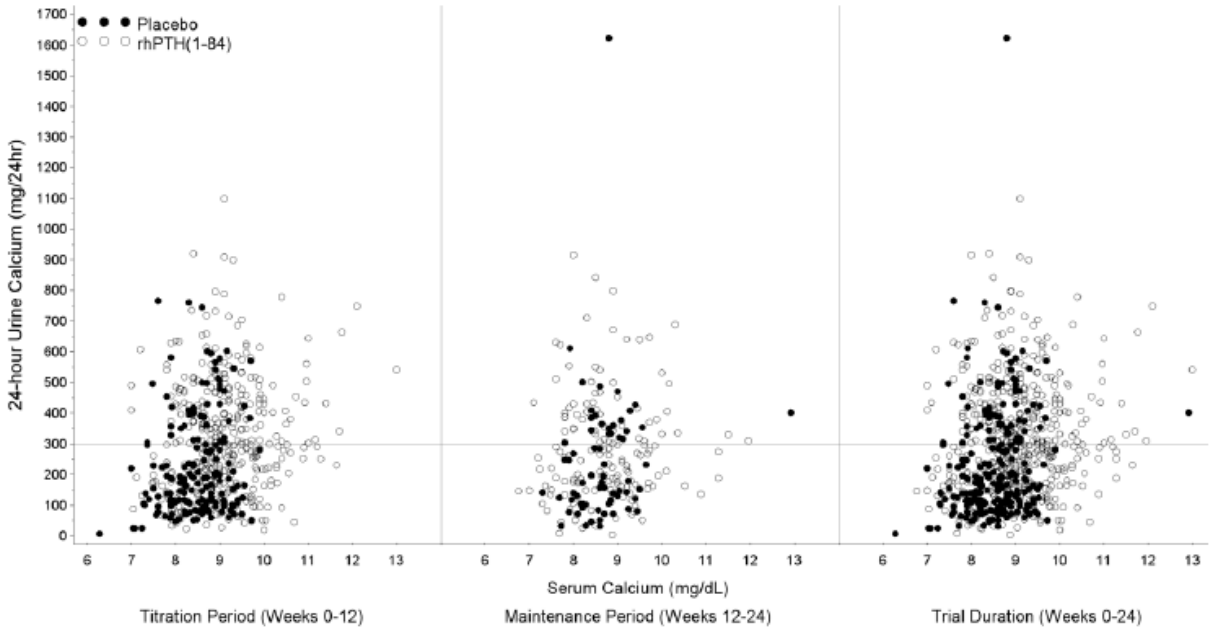


From Applicant's Submission dated May 31, 2014, Figure 3b

During the titration period, there are 181 data points in the placebo group, representing 39 subjects. There are 399 datapoints in the Natpara group, representing 84 subjects. During the maintenance period, there are 69 data points in the placebo group, representing 34 subjects. There are 161 data points in the Natpara group, representing 79 subjects. Within the entire trial duration, there are 250 data points in the placebo group, representing 39 subjects. There are 560 data points in the Natpara group, representing 84 subjects.

24 hr. urine calcium ULN=300mg/24 hr

Figure 8 24-hour Urine Calcium (mg/24hr) and Serum Calcium (mg/dL) by Study Period—ITT Population



From Applicant's Submission dated May 31, 2014, Figure 4b

During the titration period, there are 173 data points in the placebo group, representing 39 subjects. There are 383 data points in the Natpara group, representing 84 subjects. During the maintenance period, there are 67 data points in the placebo group, representing 34 subjects. There are 152 data points in the Natpara group, representing 79 subjects. Within the entire trial duration, there are 240 data points in the placebo group, representing 39 subjects. There are 535 data points in the Natpara group, representing 84 subjects.

24 hr. urine calcium ULN=300mg/24 hr

B. Serum Calcium and Serum Phosphorus Values During the Pivotal Trial

Table 26 Analysis of Albumin Corrected Serum Total Calcium Concentration– Intent-to-Treat Population

	Placebo N=40	**NPSP558 N=84**
Baseline		
n	40	84
Mean (SD)	8.6 (0.6)	8.5 (0.8)
Median	8.6	8.5
Min, Max	7.2, 9.8	5.2, 11.3
Week 4		

n	38	79
Mean (SD)	8.2 (0.5)	8.9 (0.9)
Median	8.2	8.7
Min, Max	7.4, 9.5	7.2, 12.5
Week 8		
n	38	82
Mean (SD)	8.2 (0.6)	8.7 (0.9)
Median	8.2	8.7
Min, Max	6.7, 9.2	6.6, 11.4
Week 12		
n	32	81
Mean (SD)	8.3 (0.5)	8.8 (0.8)
Median	8.3	8.8
Min, Max	7.1, 9.3	7, 10.6
Week 16		
n	34	77
Mean (SD)	8.2 (0.6)	8.5 (0.8)
Median	8.3	8.6
Min, Max	7.2, 10.2	6.5, 10.6
Week 24		
n	33	78
Mean (SD)	8.4 (0.9)	8.3 (0.9)
Median	8.3	8.3
Min, Max	7.4, 12.7	5.5, 11.5
EOT		
n	40	84
Mean (SD)	8.4 (0.9)	8.4 (0.9)
Median	8.3	8.3
Min, Max	7.1, 12.7	6.8, 11.5

From Applicant's Submission dated May 28, 2014, Table B-14.2.3.8

Table 27 Analysis of Phosphorus Levels During the Pivotal Trial—ITT Population

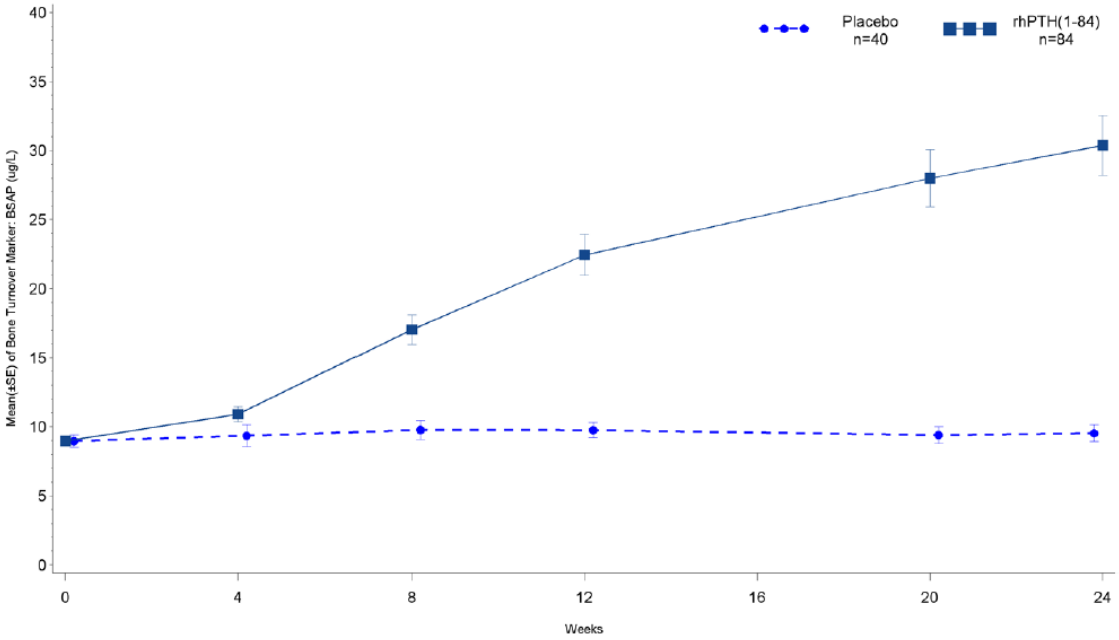
	Placebo N=40	**NPSP558 N=84**
Baseline		
n	40	84
Mean (SD)	4.5 (0.7)	4.5 (0.7)
Median	4.5	4.5
Min, Max	3.3, 6.3	3.1, 6

Week 4		
n	38	79
Mean (SD)	4.5 (0.6)	4 (0.8)
Median	4.6	4
Min, Max	3.2, 5.6	2.2, 6.6
Week 8		
n	38	82
Mean (SD)	4.6 (0.6)	4.1 (0.7)
Median	4.7	3.9
Min, Max	3.3, 6	2.8, 5.8
Week 12		
n	32	80
Mean (SD)	4.5 (0.6)	4 (0.7)
Median	4.6	4
Min, Max	3.4, 5.7	2.4, 5.7
Week 16		
n	34	76
Mean (SD)	4.6 (0.5)	4.0 (0.6)
Median	4.6	3.9
Min, Max	3.5, 5.4	2.4, 5.4
Week 24		
n	33	78
Mean (SD)	4.5 (0.5)	4 (0.7)
Median	4.5	4
Min, Max	3.6, 5.4	2.6, 6

From Applicant's Submission dated May 28, 2014, Table B-14.3.3.2.2

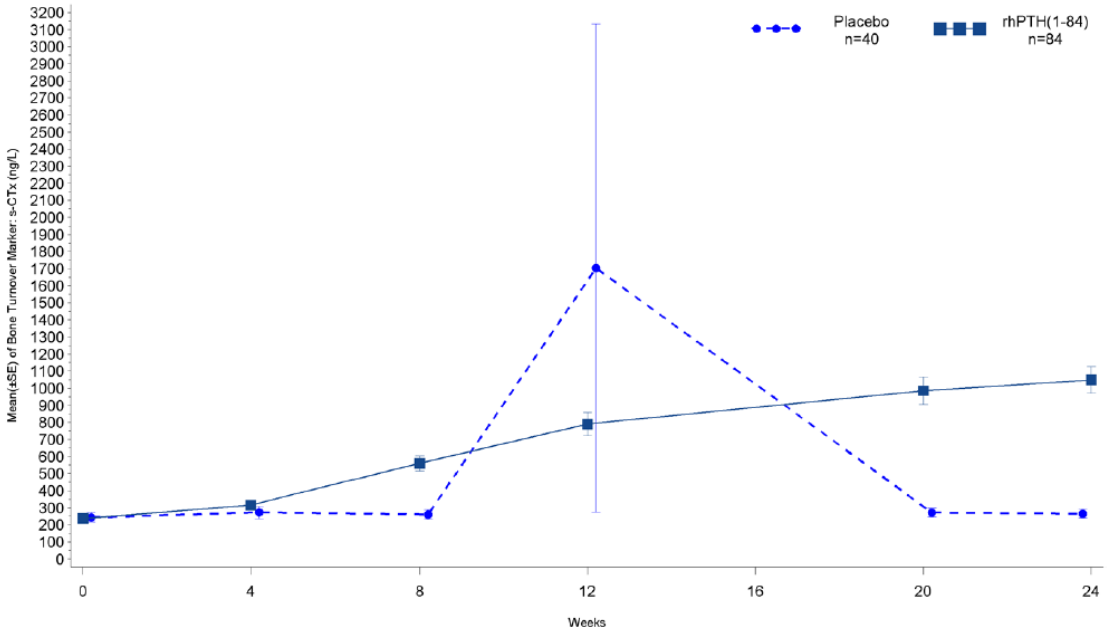
C. Bone Markers in the Pivotal Trial

Figure 9 Mean (±SE) of Bone Specific Alkaline Phosphatase (µg/L) by Trial Week in Trial 040—ITT Population



From Applicant's Submission dated June 2, 2014, Figure 1b

Figure 10 Mean (±SE) of s-CTx (ng/L) by Trial Week in Trial 040—ITT Population

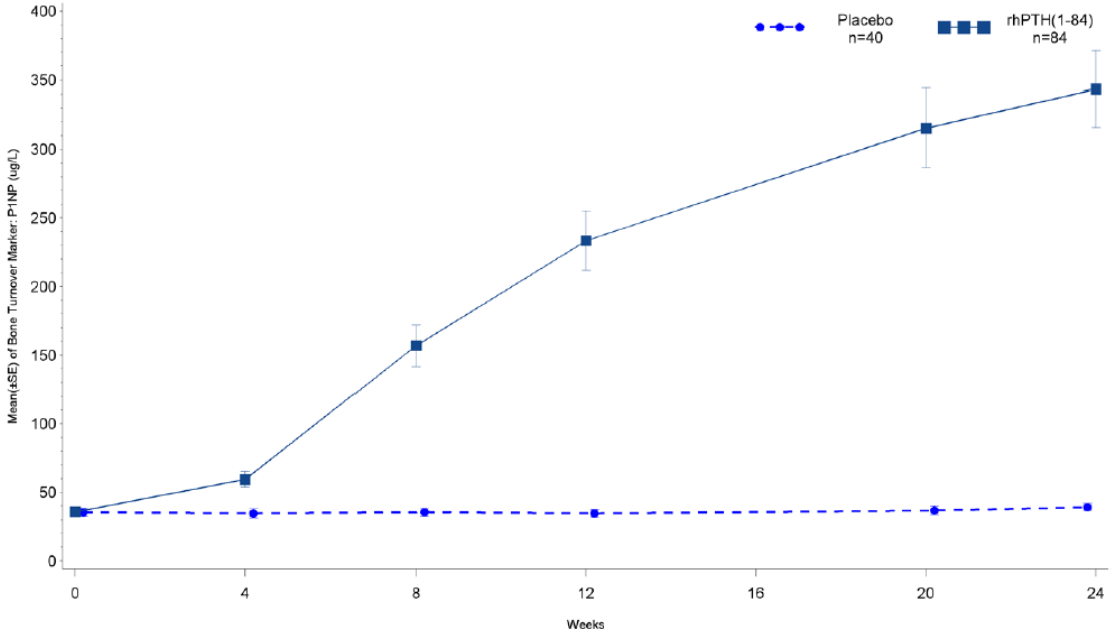


CTx = C-terminal cross-linking telopeptides of type I collagen

From Applicant's Submission dated June 2, 2014, Figure 2.1b

One subject had a value of 46,000 at Week 12 due to a lab error.

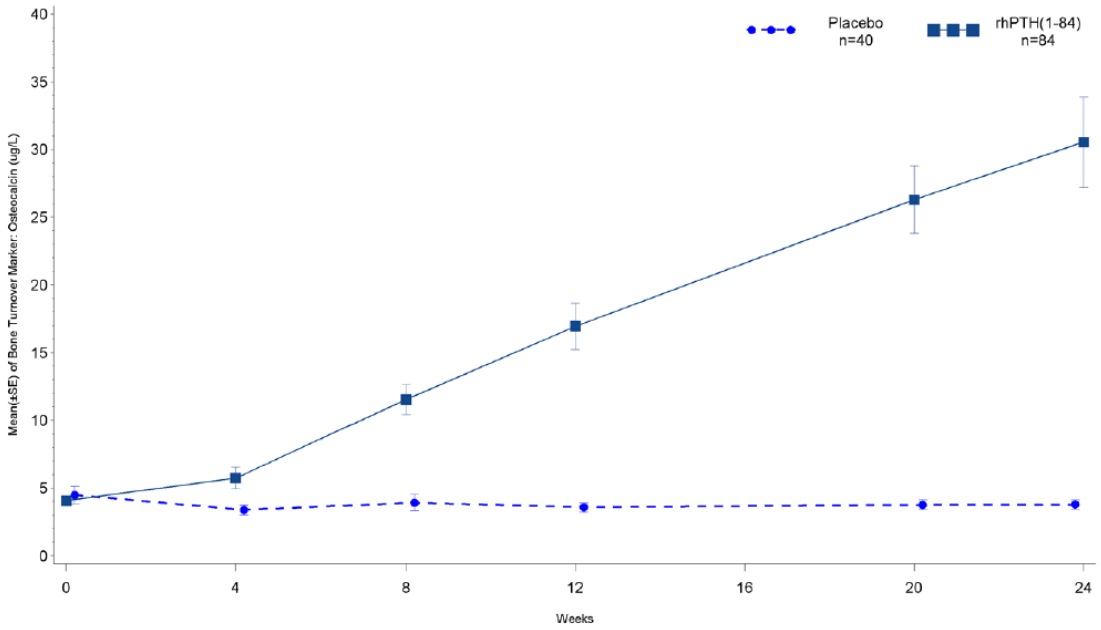
Figure 11 Mean (±SE) of P1NP (ug/L) by Trial Week in Trial 040—ITT Population



P1NP = N-terminal cross-linking propeptides of type I procollagen

From Applicant's Submission dated June 2, 2014, Figure 3b

Figure 12 Mean (±SE) of osteocalcin (ug/L) by Trial Week Trial 040—ITT Population



From Applicant's Submission dated June 2, 2014, Figure 4b

D. DXA data for Pivotal Trial

Table 28 Change in Bone Mineral Density at Week 24—ITT Population

	Placebo N=40	**rhPTH(1-84) N=84**
	Actual Value	**Actual Value**
Lumbar Spine (L1-L4)		
Baseline		
n	39	83
Mean (SD)	1.2 (0.27)	1.24 (0.19)
Median	1.2	1.25
Min, Max	0.69, 2.24	0.80, 1.73
Week 24		
n	30	71
Mean (SD)	1.2	1.22 (0.19)
Median	1.13	1.21
Min, Max	0.72, 2.2	0.81, 1.66
EOT		
n	30	73

Mean (SD)	1.19 (0.28)	1.23 (0.12)
Median	1.13	1.21
Min, Max	0.72, 2.20	0.52, 1.66
Hip—Total		
Baseline		
n	39	83
Mean (SD)	1.07 (0.20)	1.09 (0.17)
Median	1.08	1.10
Min, Max	0.71, 1.48	0.69, 1.50
Week 24		
n	30	72
Mean (SD)	1.05 (0.18)	1.07 (0.16)
Median	1.03	1.09
Min, Max	0.75, 1.34	0.70, 1.47
EOT		
n	30	74
Mean (SD)	1.05 (0.18)	1.07 (0.16)
Median	1.03	1.09
Min, Max	0.75, 1.34	0.69, 1.47
Hip—Trochanter		
Baseline		
n	39	83
Mean (SD)	0.84 (0.18)	0.86 (0.15)
Median	0.84	0.87
Min, Max	0.55, 1.23	0.56, 1.26
Week 24		
n	30	72
Mean (SD)	0.83 (0.17)	0.83 (0.14)
Median	0.81	0.83
Min, Max	0.58, 1.19	0.59, 1.19
EOT		
n	30	74
Mean (SD)	0.83 (0.167)	0.83 (0.14)
Median	0.81	0.83
Min, Max	0.58, 1.19	0.59, 1.19
Hip—Intertrochanter		
Baseline		
n	39	83
Mean (SD)	1.26 (0.23)	1.28 (0.20)
Median	1.29	1.28
Min, Max	0.82, 1.76	0.68, 1.78
Week 24		
n	30	72
Mean (SD)	1.24 (0.22)	1.25 (0.20)
Median	1.21	1.25

Min, Max	0.84, 1.76	0.67, 1.78
EOT		
n	30	74
Mean (SD)	4.24 (0.22)	1.25 (0.20)
Median	1.21	1.24
Min, Max	0.84, 1.76	0.67, 1.78
Hip—Ward's Triangle		
Baseline		
n	39	83
Mean (SD)	0.83 (0.25)	0.89 (0.23)
Median	0.85	0.88
Min, Max	0.26, 1.35	0.51, 1.54
Week 24		
n	30	72
Mean (SD)	0.80 (0.23)	0.86 (0.23)
Median	0.78	0.83
Min, Max	0.28, 1.30	0.51, 1.50
EOT		
n	30	74
Mean (SD)	0.80 (0.23)	0.86 (0.22)
Median	0.78	0.83
Min, Max	0.28, 1.30	0.51, 1.5
Hip—Femoral Neck		
Baseline		
n	39	83
Mean (SD)	0.98 (0.23)	1.01 (0.19)
Median	0.96	0.99
Min, Max	0.50, 1.48	0.67, 1.5
Week 24		
n	30	72
Mean (SD)	0.94 (0.20)	0.98 (0.19)
Median	0.88	0.97
Min, Max	0.51, 1.32	0.62, 1.46
EOT		
n	30	74
Mean (SD)	0.94 (10.20)	0.98 (0.19)
Median	0.88	0.97
Min, Max	0.54, 1.32	0.62, 1.46
Distal One Third Radius		
Baseline	40	83
n	0.76 (0.12)	0.79 (0.12)
Mean (SD)	0.74	0.78
Median	0.45, 1.07	0.57, 1.19
Min, Max		
Week 24		

n	29	70
Mean (SD)	0.75 (0.10)	0.78 (0.11)
Median	0.75	0.77
Min, Max	0.44, 0.96	0.55, 1.01
EOT		
n	29	72
Mean (SD)	0.75 (0.10)	0.78
Median	0.75	0.77
Min, Max	0.44, 0.96	0.55, 1.01

From Applicant's Submission dated June 23, 2014

Table 29 Analysis of Change in DXA T-Score at Week 42 in Trial 040, ITT Population

	Placebo N=40	**rhPTH(1-84) N=84**
	Actual Value	**Actual Value**
Lumbar Spine (L1-L4)		
Baseline		
n	39	82
Mean (SD)	0.86 (2.33)	1.16 (1.55)
Median	0.59	1.15
Min, Max	-3.26, 10.87	-2.21, 4.55
Week 24		
n	20	71
Mean (SD)	0.82 (2.42)	0.98
Median	0.36	0.99
Min, Max	-3.0, 10.47	-2.08, 4.45
EOT		
n	30	73
Mean (SD)	0.82 (24.42)	1.03 (1.58)
Median	0.36	0.99
Min, Max	-3.0, 10.47	-2.08, 4.84
Hip—Total		
Baseline		
n	39	82
Mean (SD)	0.68 (1.41)	0.79 (1.22)
Median	0.63	0.73
Min, Max	-2.17, 3.29	-2.11, 3.9
Week 24		
n	30	72
Mean (SD)	0.53 (1.35)	0.61 (1.22)
Median	0.49	0.63
Min, Max	-2.07, 3.29	-2.06, 3.65
EOT		

n	30	74
Mean (SD)	0.53 (1.35)	0.60 (1.2)
Median	0.49	0.58
Min, Max	-2.07, 3.29	-2.06, 3.65
Hip—Trochanter		
Baseline		
n	39	82
Mean (SD)	0.63 (1.47)	0.71 (1.2)
Median	0.53	0.67
Min, Max	-2.2, 3.3.87	-2.56, 3.3
Week 24		
n	30	72
Mean (SD)	0.51 (1.43)	0.50 (1.17)
Median	0.25	0.51
Min, Max	-2.03, 3.97	-2.25, 3.05
EOT		
n	30	74
Mean (SD)	0.51 (1.43)	0.49 (1.15)
Median	0.25	0.51
Min, Max	-2.03, 3.97	-2.25, 3.05
Hip—Intertrochanter		
Baseline		
n	23	49
Mean (SD)	0.6 (1.31)	0.72 (1.09)
Median	0.39	0.58
Min, Max	-1.81, 3.0	-2.74, 2.59
Week 24		
n	18	41
Mean (SD)	0.55 (1.18)	0.59 (1.13)
Median	0.36	0.53
Min, Max	-1.13, 3.06	-2.78, 2.52
EOT		
n	18	45
Mean (SD)	0.55 (1.18)	0.56 (1.12)
Median	0.36	0.51
Min, Max	-1.13, 3.06	-2.78, 2.52
Hip—Ward's Triangle		
Baseline		
n	39	82
Mean (SD)	0.16 (1.77)	0.57 (1.77)
Median	0.12	0.5
Min, Max	-4.07, 2.99	-2.33, 4.86
Week 24		
n	30	72
Mean (SD)	-0.06 (1.67)	0.40 (1.77)

Median	0.11	0.06
Min, Max	-3.85, 2.68	-2.41, 4.55
EOT		
n	30	74
Mean (SD)	-0.06 (1.67)	0.4 (1.75)
Median	0.11	0.06
Min, Max	-3.85, 2.68	-2.41, 4.55
Hip—Femoral Neck		
Baseline		
n	39	82
Mean (SD)	0.38 (1.59)	0.54 (1.37)
Median	0.21	0.53
Min, Max	-3.14, 3.51	-1.92, 3.52
Week 24		
n	30	72
Mean (SD)	0.10 (1.37)	0.34 (1.35)
Median	0.07	0.22
Min, Max	-2.75, 2.66	-2.09, 3.11
EOT		
n	30	74
Mean (SD)	0.10 (1.37)	0.35 (1.34)
Median	0.07	0.29
Min, Max	-2.75, 2.66	-2.09, 3.11
Distal One Third Radius		
Baseline		
n	40	82
Mean (SD)	-0.34 (1.03)	-0.11 (0l99)
Median	-0.13	0.01
Min, Max	-4.08, 1.32	-3.56, 1.84
Week 24		
n	29	70
Mean (SD)	-0.40 (1.13)	-0.16 (1.04)
Median	-0.29	-0.07
Min, Max	-4.18, 1.74	-3.8, 1.84
EOT		
n	29	72
Mean (SD)	-0.40 (1.14)	-0.16 (1.03)
Median	-0.29	-0.07
Min, Max	-4.18, 1.75	-3.8, 1.84

From Applicant's Submission dated June 23, 2014

Table 30 Analysis of Change in DXA Z-Score at Week 24 in Trial 040, ITT Population

	Placebo **N=40**	**rhPTH(1-84)** **N=84**

	Actual Value	Actual Value
Lumbar Spine (L1-L4)		
Baseline		
n	39	83
Mean (SD)	1.61 (2.24)	1.67 (1.43)
Median	1.35	1.65
Min, Max	-1.63, 12.06	-1.84, 4.99
Week 24		
n	30	71
Mean (SD)	1.68 (2.39)	1.55 (1.38)
Median	1.32	1.58
Min, Max	-1.52, 11.7	-1.21, 4.74
EOT		
n	30	73
Mean (SD)	1.68 (2.39)	1.61 (1.42)
Median	1.33	1.6
Min, Max	-1.51, 11.7	-1.21, 5.19
Hip—Total		
Baseline		
n	39	83
Mean (SD)	1.23 (1.29)	1.22 (1.08)
Median	0.98	1.14
Min, Max	-1.27, 3.82	-1.46, 3.99
Week 24		
n	30	72
Mean (SD)	1.16 (1.29)	1.05 (1.08)
Median	1.01	0.92
Min, Max	-1.13, 3.85	-1.35, 3.75
EOT		
n	30	74
Mean (SD)	1.16 (1.29)	1.05 (1.07)
Median	1.01	0.89
Min, Max	-1.13, 3.85	-1.35, 3.75
Hip—Trochanter		
Baseline		
n	39	82
Mean (SD)	1.15 (1.36)	1.11 (1.08)
Median	1..04	0.98
Min, Max	-1.27, 4.4	-2.06, 3.48
Week 24		
n	30	72
Mean (SD)	1.12	0.92 (1.04)
Median	0.93	0.78
Min, Max	-1.18, 4.53	-1.72, 3.24

EOT		
n	30	74
Mean (SD)	1.12 (1.39)	0.92 (1.03)
Median	0.93	0.78
Min, Max	-1.18, 4.53	--1.72, 3.24
Hip—Intertrochanter		
Baseline		
n	23	49
Mean (SD)	1.0 (1.22)	1.0(0.97)
Median	0.98	0.97
Min, Max	-1.02, 3.35	-1.56, 2.61
Week 24		
n	18	43
Mean (SD)	1.0 (1.14)	0.87 (1.01)
Median	0.84	0.97
Min, Max	-0.99, 3.42	-1.56, 2.61
EOT		
n	18	45
Mean (SD)	1.0 (1.14)	0.84 (1.0)
Median	0.84	0.93
Min, Max	-0.99, 3.42	-1.56, 2.61
Hip—Ward's Triangle		
Baseline		
n	39	82
Mean (SD)	1.31 (1.47)	1.55 (1.61)
Median	1.54	1.41
Min, Max	-1.88, 3.62	-1.68, 5.49
Week 24		
n	30	72
Mean (SD)	1.26 (1.48)	1.4 (1.58)
Median	1.13	1.34
Min, Max	-1.63, 3.6	-1.71, 4.95
EOT		
n	30	74
Mean (SD)	1.26 (1.48)	1.42 (1.57)
Median	1.13	1.39
Min, Max	-1.63, 3.6	-1.71, 4.95
Hip—Femoral Neck		
Baseline		
n	39	83
Mean (SD)	1.16 (1.34)	1.21 (1.21)
Median	1.04	1.06
Min, Max	-1.69, 4.16	-1.17, 4.34
Week 24		
n	30	72

Mean (SD)	0.99 (1.21)	1.02 (1.20)
Median	1.12	0.86
Min, Max	1.27, 3.81	-1.18, 3.65
EOT		
n	30	74
Mean (SD)	0.99 (1.21)	1.04 (1.19)
Median	1.12	0.92
Min, Max	1.27, 3.81	-1.18, 3.65
Distal One Third Radius		
Baseline		
n	40	83
Mean (SD)	0.36 (1.02)	0.39 (1.03)
Median	0.44	0.39
Min, Max	-2.52, 2.13	-3.56, 2.46
Week 24		
n	29	70
Mean (SD)	0.40 (1.15)	0.37 (1.09)
Median	0.23	0.44
Min, Max	-2.57, 2.58	-3.8, 2.63
EOT		
n	29	72
Mean (SD)	0.4 (1.15)	0.38 (1.08)
Median	0.23	0.44
Min, Max	-2.57, 2.58	-3.8, 2.63

From Applicant's Submission dated June 23, 2014

E. Other Laboratory Measurements in the Pivotal Trial

Serum 1,25-Dihydroxyvitamin D and Serum 25-Hydroxyvitamin D

Serum 1,25-vitamin D levels minimally changed in both groups by Week 24 (even in the face of decreasing active vitamin D/Vitamin D analog in the NPSP558 group). In contrast, the mean 25(OH)-vitamin D level decreased markedly in the NPSP558 group, while it changed minimally in the placebo group. At Week 24, the change from baseline in mean serum 25(OH)-vitamin D levels was -11.23 (±19.02) ng/mL in the NPSP558 group compared to -1.38 (±13.15) ng/mL in the placebo group. The Applicant explains this decrease by the PTH-induced conversion of 25(OH) vitamin D into 1,25-dihydroxyvitamin D.

Table 31 Summary of Serum 1,25-Dihyroxyvitamin D and Serum 25-Hydroxyvitamin D by Visit in Trial 040—Safety Population

	Placebo	NPSP558

	N=40		N=84	
Parameter (Unit) Visit	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Serum 1,25-dihydroxyvitamin D (pg/mL)				
Baseline				
n	40		82	
mean (SD)	32.7 (11.5)		33.7 (21.2)	
median	30		30	
min, max	14, 61		8, 148	
Week 24				
n	28	28	71	70
mean (SD)	33.6 (18.8)	-0.3 (17.3)	33 (12.9)	1 (20)
median	28	-1.0	33	1
min, max	8, 95	-27, 46	9, 60	-75, 46
EOT				
n	35	35	80	78
mean (SD)	31.9 (17.5)	-1.8 (16.4)	32.4 (12.8)	-1 (22.7)
median	28	-4	32.5	0.5
min, max	8, 95	-27, 46	9, 60	-97, 46
Serum 25-hydroxyvitamin D (ng/mL)				
Baseline				
n	40		84	
mean (SD)	44.5 (19)		42.3 (14.8)	
median	38		38.5	
min, max	25, 104		11, 109	
Week 24				
n	31	31	78	78
mean (SD)	42.6 (14.2)	-1.3 (13.5)	32.6 (11.4)	-10 (15.7)
median	40	3	29	-10
min, max	17, 78	-41, 18	18, 82	-82, 46
EOT				
n	40	40	84	84
mean (SD)	41.8 (13)	-2.7 (14.6)	32.4 (11.1)	-9.8 (15.3)
median	39	2	29	-9.5
min, max	17, 78	-51, 18	18, 82	-82, 46

Applicant's Submission dated May 28, 2014 Table B-14.3.6

F. Subjects who had a Calcium-Phosphate Product Greater Than 55 mg^2/dL^2 at Week 24 in Trial 040

The following analyses were done by the Applicant in response to the Division's request. Below is a scatterplot for calcium-phosphate product for the pivotal trial. Included only are individual

pairs of calcium and phosphate measurements that were measured on the same day, and the data are presented for titration and maintenance periods.

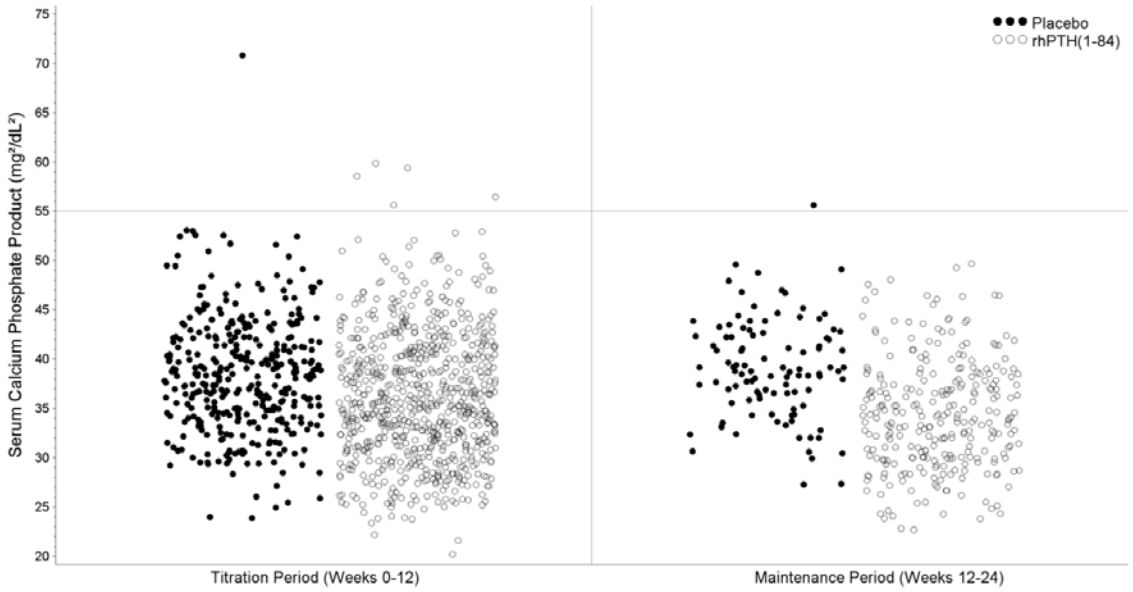
At baseline, no subject in the placebo group and one subject in the NPSP558 group had a calcium-phosphate product greater than 55 mg^2/dL^2. The following table summarizes subjects with a high calcium-phosphate product during titration, reflected in the data points below. There were no Natpara-treated subjects with an elevated product during the maintenance period.

Table 32 Subjects with a high calcium-phosphate product in Trial 040

Subject ID	Treatment	Visit (week of treatment)	Calcium-phosphate product
0002-0003	Natpara	2	59.85
2001-0007	Natpara	4	56.45
2001-0009	Natpara	8 (unscheduled)	68.56
8001-0001	Natpara	3	55.61
8002-0001	Natpara	4	59.39
1014-0003	Placebo	8 (unscheduled)	70.81

From Applicant's Submission dated June 6, 2014

Figure 13 Serum Calcium Phosphate Product (mg^2/dL^2) by Study Period in Trial 040



Note:During the Titration Period, there are 358 data points in the Placebo group, representing 40 subjects. There are 736 data points in the rhPTH (1-84) group, representing 84 subjects. During the Maintenance Period, there are 104 data points in the Placebo group, representing 35 subjects. There are 278 data points in the rhPTH (1-84) group, representing 79 subjects Baseline values are excluded from the analysis. Week 12 is included in the Titration Period.
Upper Limit of Normal = 55 mg²/dL²

From Applicant's Submission Dated May 31, 2014

G. Trial 007

This was a short-term trial exploring a lower dose of Natpara. The lowest dose allowed in the pivotal trial was 50 µg. After the pivotal trial was completed, the Applicant conducted this randomized, dose-blinded trial to explore the safety and efficacy of the 25 µg dose compared to 50 µg.

Subjects were previously in an NPSP558 trial and were randomized to receive either NPSP558 25 µg SC once daily (QD) or 50 µg SC QD in a fixed-dose fashion.

The goal of supplement titration was to reduce the need for calcitriol and oral calcium (carbonate or citrate) supplementation to as low as safely possible, while maintaining total serum calcium ideally between 8.0 and 9.0 mg/dL. Down-titration of calcitriol and calcium was undertaken by the investigator based on total serum calcium concentrations using an algorithm described in the Titration Guideline in which it was recommended that calcitriol be reduced first by up to 50%, followed by a reduction of up to 50% in oral calcium supplementation. The order and magnitude of subsequent reductions in either calcitriol or oral calcium supplementation was left to the investigator's discretion, based on individual subject response.

Study drug was to be stopped of the pre-dose calcium level remained above the ULN for 2 more consecutive safety assessments (no more than 5 days apart), following withdrawal of all supplements. If any calcium level was above 11.9 mg/dL, treatment with study drug was to be stopped immediately. When calcium levels returned to normal, the decision to restart NPSP558 was done in consultation with the medical monitor.

The primary efficacy endpoint was the proportion of subjects in the NPSP558 25 μg and NPSP558 50 μg dosage groups that by Week 8 (Visit 4) achieved each of the following:

• A reduction in oral calcium supplementation to ≤ 500 mg/day and

• A reduction in calcitriol dose to ≤ 0.25 μg/day and

• An albumin-corrected total serum calcium level between 7.5 mg/dL and the upper limit of normal (ULN) for the central laboratory

The components of this endpoint were somewhat different than those in the pivotal trial, which focused on reductions of 50% for calcium and vitamin D supplements.

The primary analysis of the primary endpoint in this 8-week trial was based on the investigator-prescribed data, shown below. Four subjects in the 25 μg group and six subjects in the 50 μg group met the primary endpoint. There was no statistically significant treatment difference between the two groups.

If patient diary data is used, only 1 subject in each group met the primary endpoint.

Primary Response Rate at Week 8 Based on Investigator-prescribed Data for Trial 007 –ITT Population

	rhPTH (1-84) 25 μg N=19		**rhPTH (1-84) 50 μg N=23**			
Status	n (%)	(95% CI)	n (%)	(95% CI)	Treatment Difference (95% CI)	p-value
Responder Non-responder	4 (21.1) 15 (78.9)	(6.1, 45.6)	6 (26.1) 17 (73.9)	(10.2, 48.4)	5.0 (-20.6, 30.7)	>0.999

From Applicant's Submission dated June 5, 2014, Table B-14.2.1.1.1

Percentages are based on the number of ITT subjects in each treatment arm. Responder is defined as subjects whose daily calcium supplementation at Week 8 was ≤500 mg/day and the daily calcitriol dose was ≤0.25 μg/day and the albumin-corrected calcium level at Week 8 was between 7.5 mg/dL and the upper limit of normal. Subjects who terminated early or had missing lab data at Week 8 were considered non-responders.

The secondary endpoint in this trial was the response rate at Week 8 based on the proportion of subjects with ≥50% reductions from baseline in oral calcium and calcitriol supplementation and albumin-corrected total serum calcium concentration that was normalized or maintained compared to the baseline value (≥7.5 mg/dL) and did not exceed the ULN. The table below summarizes the secondary endpoint results.

Secondary Response Rate at Week 8 Based on Investigator-prescribed Data for Trial 007—ITT Population

	rhPTH (1-84) 25 µg N=19		**rhPTH (1-84) 50 µg N=23**			
Status	n (%)	(95% CI)	n (%)	(95% CI)	Treatment Difference (95% CI)	p-value
Responder	2 (10.5)	(1.3, 33.1)	6 (26.1)	(10.2, 48.4)	15.6 (-7.1, 38.2)	0.258
Non-responder	17 (98.5)		17 (73.9)			

From Applicant's submission dated June 5, 2014, Table B-14.2.2.1.1

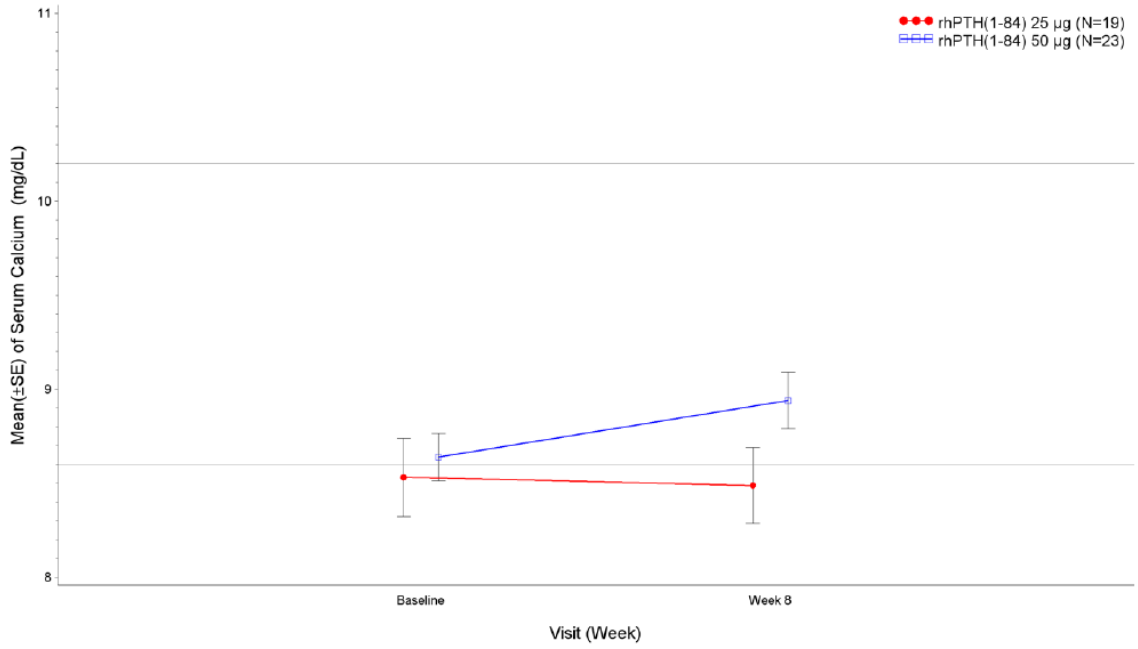
For this trial, the Applicant combined terms hypocalcemia, hypercalcemia, and hypercalciuria with blood calcium increased, blood calcium decreased, and urine calcium increased, respectively. Based on this, 3 subjects in the 25 µg group and 3 subjects in the 50 µg group experienced such an event during the treatment period.

In the 25 µg group, there was one subject with hypocalcemia and two subjects with hypercalcemia, one noted as severe. This subject was a 60 year old woman who had a baseline calcium level of 9.3 mg/dL who had severe hypercalcemia at Week 4 (maximum value of 12.3 mg/dL). She experienced no symptoms. Calcium supplementation was discontinued and study drug was interrupted on Days 30 through 32. Serum calcium returned to normal and study drug was resumed with a calcium level of 10.8 mg/dL at Week 8.

In the 50 µg group, there was one subject with hypercalcemia, one with hypocalcemia, and one with hypercalciuria.

The figure below depicts the mean change in calcium levels for both groups. The 50 µg group remained close to the lower limit of normal, while the 25 µg group was just below or at the lower limit.

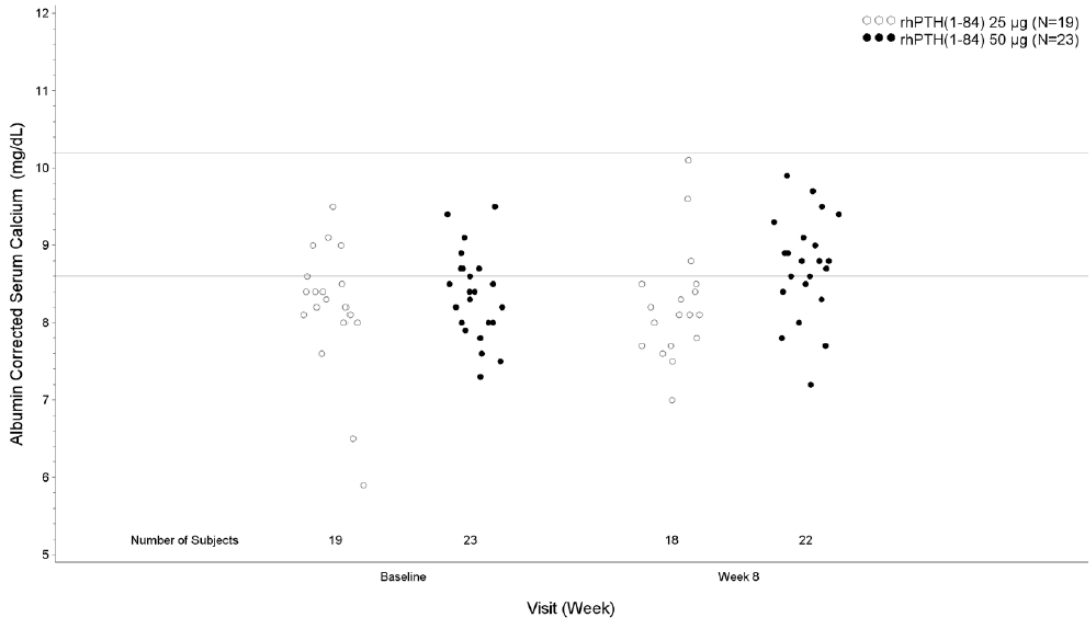
Figure 14 Mean (±SE) of Serum Calcium (mg/dL) by Visit for Trial 007



From Applicant's Submission dated June 2, 2014, Figure 1b

The figure below is a scatterplot of serum calcium at baseline and at Week 8 for both dose groups. Consistent with the figure above, there is a tendency for more hypocalcemia in the lower dose group at Week 8.

Figure 15 Scatterplot of Albumin-corrected Serum Calcium (mg/dL) at baseline and at Week 8 in Trial 007-ITT Population



From Applicant's Submission dated June 2, 2014, Figure 2b

H. Trial 008

This is a long-term, open-label trial of NPSP558 in adults with hypoparathyroidism. There is no control group. While the focus of this trial was on long-term safety and tolerability, a subject was considered a responder if the met the following 3 criteria at Week 52:

A ≥50% reduction from baseline in dose of oral calcium supplementation or an oral calcium dose of ≤500 mg

AND

A ≥50% reduction from baseline in dose of oral calcitriol supplementation or an oral calcitriol dose of ≤0.25 µg

AND

An albumin-corrected total serum calcium concentration that is normalized or maintained compared to the baseline value (≥7.5 mg/dL) and does not exceed the ULN of the central laboratory.

To be eligible, subjects had to have completed Trial 007 (RELAY) and/or completed the pivotal trial 040. The baseline parameters for the efficacy variables for RACE were the end of study parameters from RELAY or REPLACE.

The starting doses were 25 or 50 µg, depending on an algorithm. The dose of NPSP558 could be increased in increments of 25 µg to a maximum of 100 µg at any time during the trial, with the goal of achieving or maintaining total serum calcium levels in the range of 8-9 mg/dL. The dose could be down-titrated at any time for efficacy or safety reasons.

During the first 12 months, visits were to take place at Weeks 1, 4, 8, and then every 8 weeks up to Week 48. The Week 52 was scheduled 4 weeks later.

At the end of Week 52, subjects were invited to enter a long-term extension, during which visits were to take place every 2 months.

The primary efficacy analysis was conducted at two evaluation points in this long-term trial: Week 52 and EOT, defined as the last determination of response or last available measurement during the treatment period up to the interim data cut-off date. A subject must have met all 3 criteria to have been considered a responder. The table summarizes the pre-defined responder rates at the two time points. Although this analysis represents data from an open-label without a comparator, the results are consistent with and extend the findings of the pivotal trial.

The reason for the difference between the Week 52 and EOT analysis is unclear.

Table 33 Analysis of Responder Rate Based on Investigator-prescribed Data in Trial 008

	NPSP558 (N=49)	
	n/m (%)	**(95% CI)**
Week 52		
Responder	34/45 (75.6)	(60.5, 87.1)
Non-responder	11/45 (24.4)	
End of Treatment		
Responder	25/48 (52.1)	(37.2, 66.7)
Non-responder	23/48 (47.9)	

Percentages are based on 'm', the number of ITT subjects with valid responder values available at the visit.

From Applicant's Submission dated June 2, 2014, Table B-14.2.1.1.1

The following secondary endpoints are discussed for Trial 008: change in 24-hour urinary calcium excretion, change in serum calcium, change in bone turnover markers, change in bone

mineral density, and proportion of subjects that maintained a calcium-phosphate product in the normal range of 35 to 55 mg^2/dL^2.

Mean Change from Baseline in 24-hour Urinary Calcium Excretion

At baseline (n=52), the mean (±SD) 24-hour urinary calcium excretion was 354.33 (±196.96) mg/24 hr. At Week 52 (n=48), the mean 24-hour urinary calcium excretion was 317.31 (±174) mg/24 hr.

There were 5 subjects who used calcium-sparing diuretics at baseline, and the mean 24-hour urinary calcium of these subjects was 412.80 (±268.79) mg/24 hr at baseline. At Week 52, the 24-hour urinary calcium in these subjects was still higher compared with subjects not using them (423.60 (±180.65) vs. 304.95 (171.1), respectively).

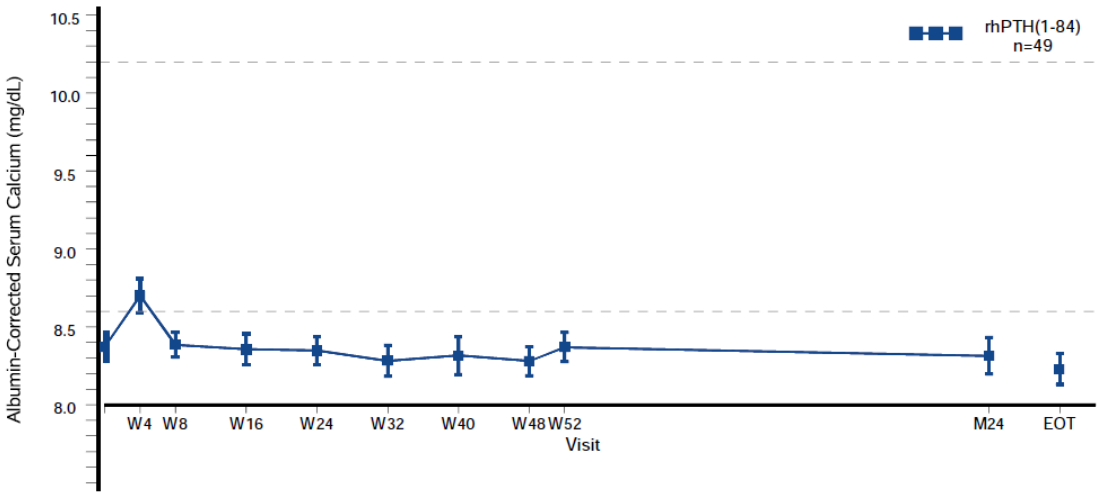
There were no subjects who had calcium-sparing diuretics added during the trial.

Change from Baseline in Albumin-corrected Total Serum Calcium

Although this secondary endpoint was presented by the Applicant as percentage change, here the mean changes in the actual calcium levels are presented.

Mean calcium levels changed little from baseline to Week 52. Mean levels at both time points were within the target range (8 to 9 mg/dL), which was slightly below the normal range of total serum calcium levels.

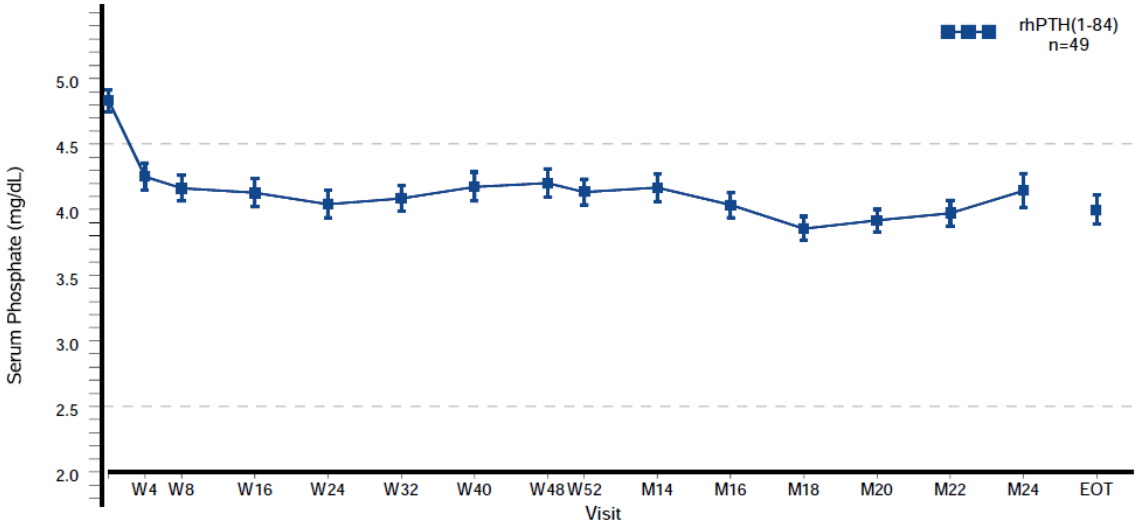
Figure 16 Mean (±SE) of Observed Values in Albumin-Corrected Serum Total Calcium by Visit in Trial 008—ITT Population



Applicant's Submission Dated June 2, 2014, Figure B-14.2.4.2

Although not a secondary endpoint, it is important to note that mean serum phosphate decreased into the range of normal during the trial.

Figure 17 Mean (±SE) of Observed Values in Serum Phosphate in Trial 008—ITT Population

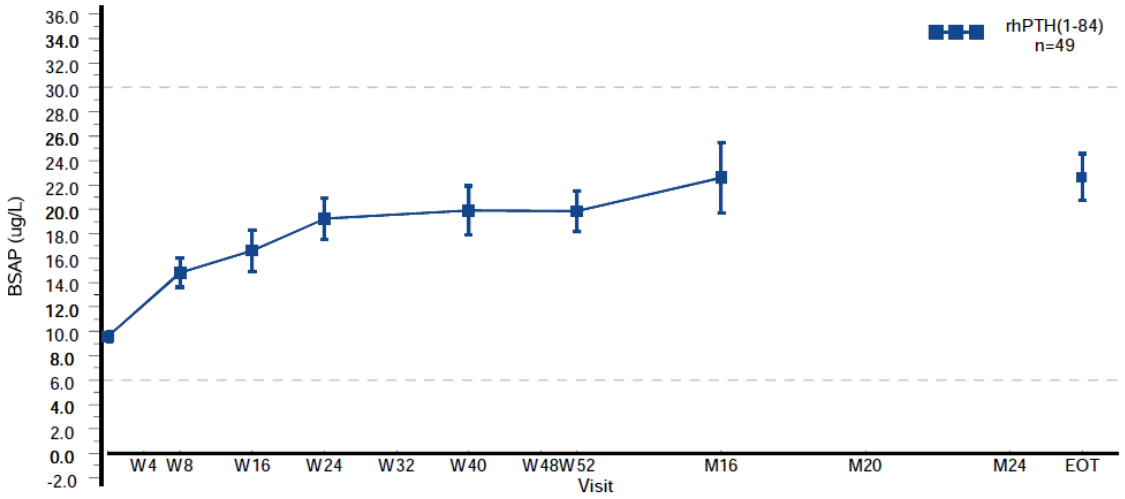


Applicant's Submission dated June 2, 2014, Figure B-14.2.6.2

Change from Baseline in Bone Turnover Markers

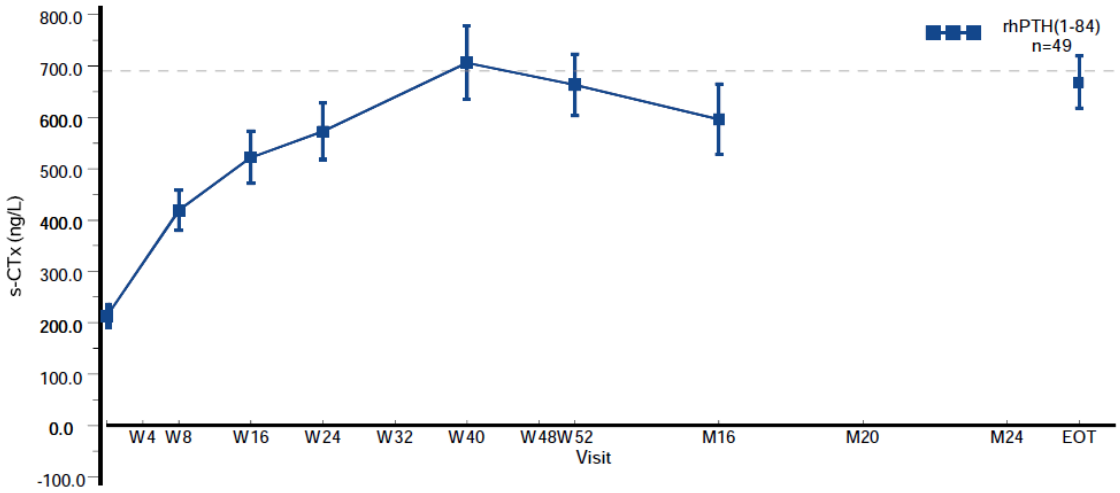
The figures below depict the changes in bone turnover markers during the 52 weeks. It should be noted that the baseline values in this trial reflected the final values from either RELAY or REPLACE, in which increases in subjects' bone markers were observed. With the exception of osteocalcin, levels of other markers appeared to plateau or decrease.

Figure 18 Mean (± SE) of Observed Values in Bone-Specific Alkaline Phosphatase (BSAP) in Trial 008– ITT Population



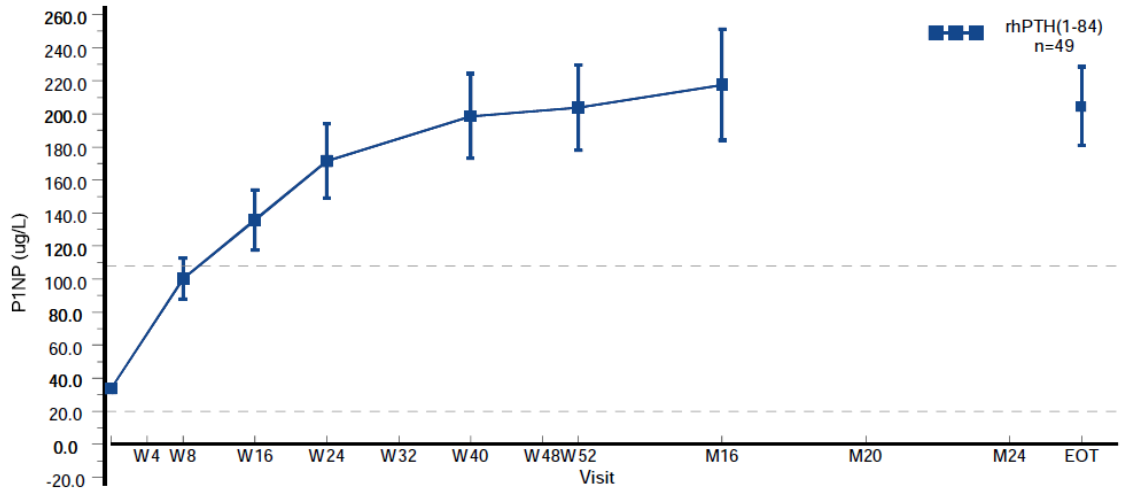
From Applicant's Submission dated June 2, 2014, Figure B-14.2.7.1.2

Figure 19 Mean (± SE) of Observed Values in Serum Carboxy-Terminal Telopeptide of Type I Collagen (s-CTx) in Trial 008 – ITT Population



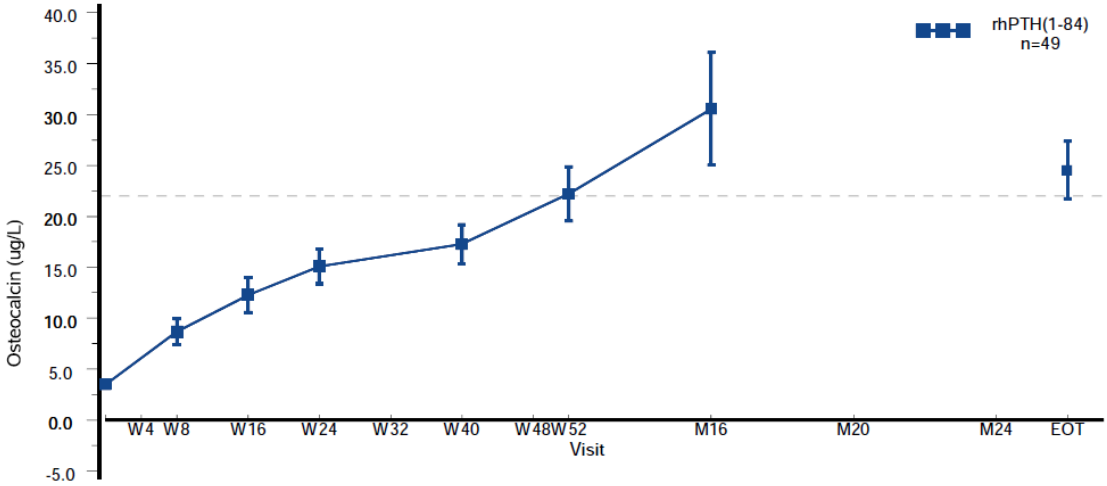
From Applicant's Submission dated June 2, 2014, Figure B-14.2.7.2.2

Figure 20 Mean (± SE) of Observed Values in Serum Procollagen Type 1 Amino-terminal Propeptide (P1NP)) in Trial 008 —ITT Population



From Applicant's Submission dated June 2, 2014, Figure B-14.2.7.3.2

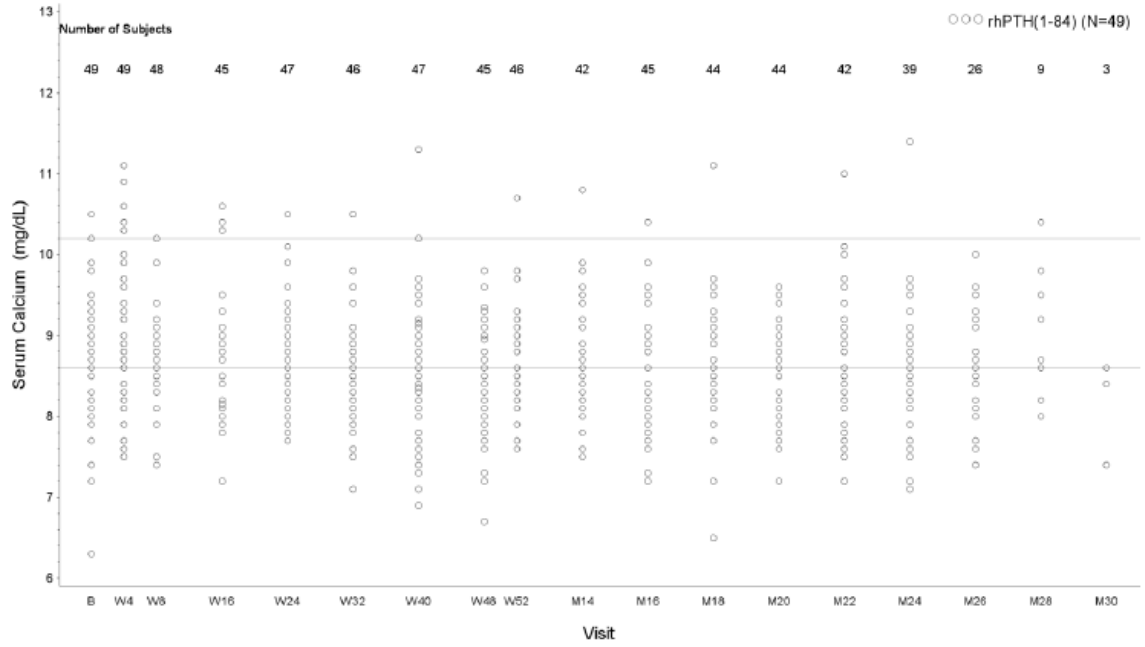
Figure 21 Mean (± SE) of Observed Values in Osteocalcin in Trial 008 —ITT Population



From Applicant's Submission dated June 2, 2014, Figure B-14.2.7.4.2

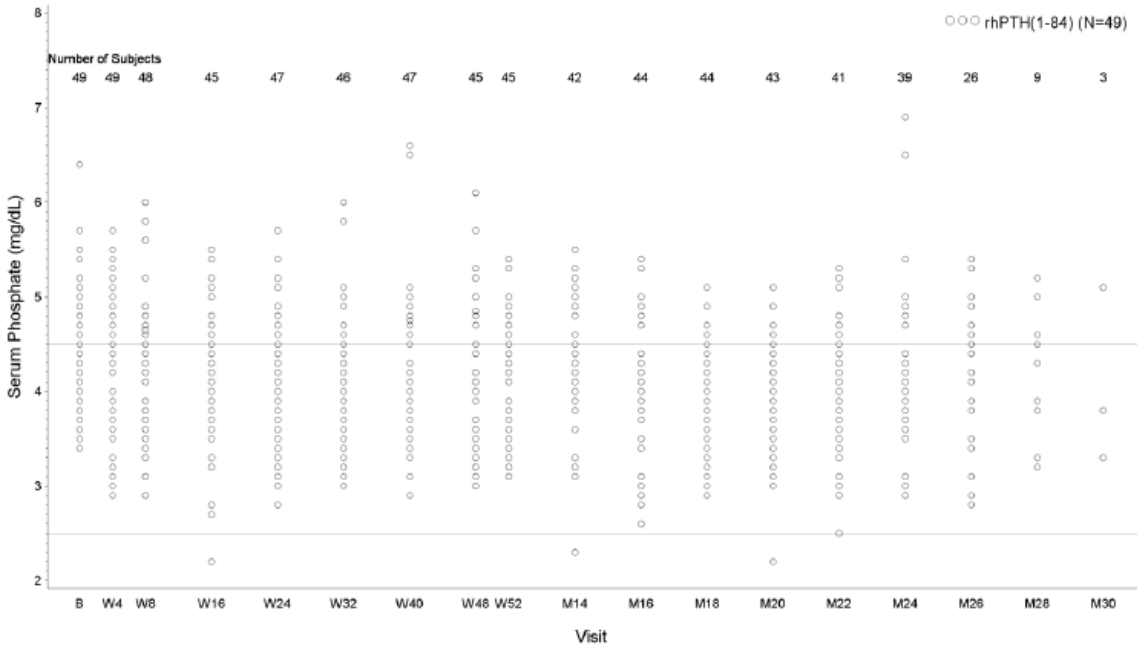
The following are scatterplots of serum calcium, serum phosphorus, and urinary calcium requested by the Division and submitted by the Applicant. By the end of the extension period, there are few subjects with these measurements.

Figure 22 Scatterplot of Serum Calcium (mg/dL) by Visit in Trial 008—ITT Population



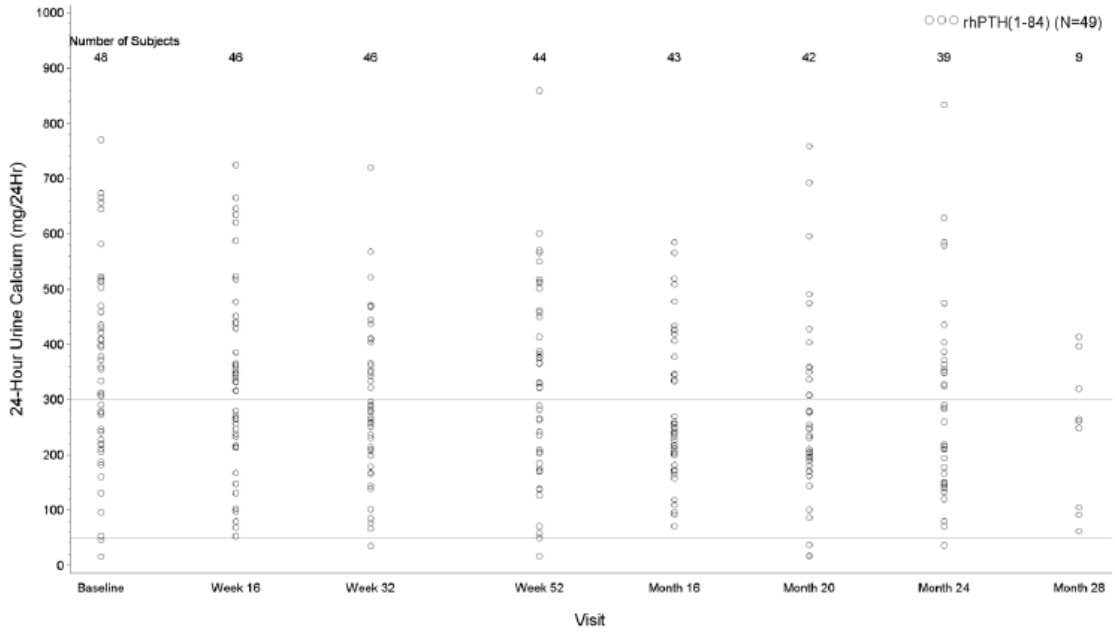
Upper Limit of Normal = 10.2 mg/dL, Lower Limit of Normal = 8.6 mg/dL

Figure 23 Scatterplot of Serum Phosphate (mg/dL) by Visit in Trial 008—ITT Population



Upper Limit of Normal = 4.5 mg/dL, Lower Limit of Normal = 2.5 mg/dL

Figure 24 Scatterplot of 24-hour Urinary Calcium, (mg/24h) by Visit) in Trial 008 —ITT Population



Upper Limit of Normal = 300 mg/24Hr, Lower Limit of Normal = 50 mg/24Hr

The following table summarizes subjects with normal or abnormal urine calcium by time. By Week 52, there was a slight increase in the percentage of subjects with normal urinary calcium. By Month 28, the number of subjects with measurements decreased sharply.

Table 34 Number (%) of Subjects with Normal of Abnormal Urine Calcium Values (mg/24 hr) by Visit in Trial 008—Safety Population

	rhPTH (1-84) N=49		
Visit	m	Normal (≤300) n (%)	Abnormal (>300) n (%)
Baseline	48	19 (39.6)	29 (60.4)
Week 16	46	19 (41.3)	27 (58.7)
Week 32	46	28 (60.9)	18 (39.1)
Week 52	44	20 (45.5)	24 (54.5)
Month 16	43	27 (62.8)	17 (37.2)
Month 20	42	28 (66.7)	14 (33.3)
Month 24	39	24 (61.5)	15 (38.5)
Month 28	9	6 (66.7)	3 (33.3)

m is the number of subjects with 24-hour urine calcium excretion tested at each visit

STATISTICAL BRIEFING MATERIAL

BLA 125511: NPSP558 (ALX1-11, rhPTH[1-84], NATPARA)
APPLICANT: NPS PHARMACEUTICALS INC.

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE MEETING

SEPTMEBER 12, 2014

Jennifer Clark, PhD
Mark Rothmann, PhD

Division of Biometrics II
Office of Biostatistics
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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1 EXECUTIVE SUMMARY

NPS Pharmaceuticals submitted RhPTH(1-84), an injected recombinant human parathyroid hormone, for the treatment of long term hypoparathyroidism. Approval is being sought for this treatment based on evaluations of change in oral calcium and vitamin D doses from baseline to Week 24 in hypoparathyroid patients.

1.1 Brief Overview of Clinical Studies

There are a total of 5 efficacy and safety studies in the NPS clinical development program which are described in Table 3 of section 2.1. Study CL1-11-040 is listed by the sponsor as the primary registration study and will be the focus for this review. This was a 24-week placebo controlled study which used a dose titration process to achieve a functioning dose for each subject by the end of the treatment period. Due to the low prevalence of hypoparathyroidism, this study had a multicenter and multinational population in order to achieve adequate statistical power. This included sites from eight countries where a total of 29 sites randomized subjects. The primary endpoint was a composite of oral calcium reduction, vitamin D reduction, and normalized serum calcium concentrations. Using the methodology described in section 3.1, we found the outcomes were better on Natpara when compared with placebo (Table 1).

Table 1: Primary Endpoint Results

	Placebo (N=40)	RhPTH(1-84) (N=84)	
	n (%)	n (%)	P
Responder	1 (3%)	46 (55%)	<.0001
Non-Responder	39 (97%)	38 (45%)	

Table 2 shows the proportion of subjects that achieved each of the three components in the primary endpoint. Those who achieve all three components in this table are presented as responders in Table 1.

Table 2: Components of the Primary Endpoint

	Placebo (N=40)	Natpara (N=84)
	n (%)	n (%)
At Least a 50% Reduction from Baseline Oral CA		
Achieved	3 (7.5%)	58 (69%)
Not Achieved	37 (92.5%)	26 (31%)
At Least a 50% Reduction from Baseline Active Vitamin D		
Achieved	18 (45%)	73 (86.9%)
Not Achieved	22 (55%)	11 (13.1%)

Serum CA between 7.5 and 10.6 mg/dL		
Achieved	35 (87.5%)	74 (88.1%)
Not Achieved	5 (12.5%)	10 (11.9%)

All five efficacy and safety studies are listed in Table 3 of section 2.1. The remaining four studies are used to provide evidence of the effectiveness of Natpara for the treatment of hypoparathyroidism as a replacement for the endogenous parathyroid hormone PTH(1-84).

1.2 Statistical Issues and Concerns

- During the review of this BLA, FDA inspections of three clinical sites were completed. One site was noted to have multiple GCP violations across several trials in this program, including study CL1-11-040. The violations called into question the completeness and reliability of the data collected at this site. After internal FDA deliberations, the data originating from this single site were deemed unreliable. Data from all other sites inspected were considered adequate and the review of the BLA did not identify any other GCP deficiencies.

- There is some concern about the appropriate range for a serum calcium concentration that would be considered a "laboratory normal range." See Section 3.3 for further details.

2 INTRODUCTION

2.1 Overview

There were five efficacy and safety studies, listed in Table 3, which were completed and submitted for review with one study designated as primary containing a placebo control arm. Only study CL1-11-040 was reviewed here for efficacy.

Table 3: Safety and Efficacy Studies in Hypoparathyroid Subjects for NATPARA (rhPTH[1-84])

	Study Objectives	Study Design and Type of Control	Test Product(s), Number of Subjects	Duration of Treatment
Placebo Controlled Study				
CL1-11-040 (REPLACE)	Efficacy and Safety	Randomized, double-blind, placebo controlled	Varying doses of 50, 75, and 100 µg SC in the thigh of rhPTH[1-84] daily, 90 or Placebo, 44	24 weeks
Dose Comparison Concurrent Controlled Study				
PAR-C10-007 (RELAY)	Efficacy and Tolerability	Ranomized, dose-blinded	Fixed doses of 25 or 50 µg SC in the thigh of rhPTH[1-84] daily, 47	8 weeks

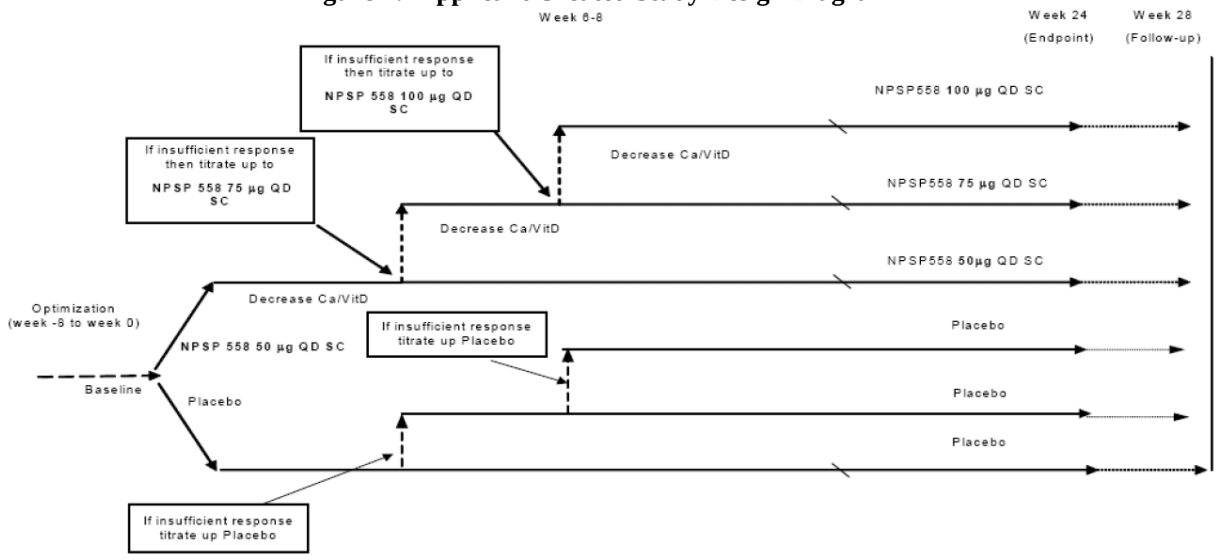
Dose Comparison Concurrent Uncontrolled Study				
PAR-C10-008 (RACE)	Safety and Tolerability	Open-Label	Varying doses of 25, 50, 75, and 100 µg SC in the thigh of rhPTH[1-84] daily, 53	12 months + extension Ongoing
Uncontrolled				
PAR-C10-009 (REPEAT)	Safety and Tolerability	Open-Label	Varying doses of 50, 75, and 100 µg SC in the thigh of rhPTH[1-84] daily, 24	24 Weeks
Investigator Initiated Trial				
Bilezikian IIT	Safety and Efficacy	Open-label study, prospective	Varying doses of 50, 75, and 100 mg SC in the thigh of rhPTH[1-84] daily or less than daily, 79	Ongoing

3 STATISTICAL EVALUATION OF EFFICACY

3.1 Study Design and Endpoints

The main study was a 6-month, multicenter, double-blind, randomized, placebo-controlled study. Since the study included one primary and three secondary efficacy endpoints, a fixed sequence test procedure was used to control the Type I error starting with the primary efficacy endpoint and then proceeding to the secondary endpoints in a pre-specified order, if any hypothesis was found to be non-significant with $p<.05$ level then any subsequent tests were not executed. Figure 1 gives an applicant created schematic of this study design.

Figure 1: Applicant Created Study Design Diagram



Baseline was defined as the last available pre-dose value. An optimization period was implemented so that all subjects were brought to a common baseline in order to ensure that subjects in both arms of the study began treatment at the same levels of calcium control; this controlled for comparisons between treatment arms. Randomization followed by a 24-week treatment period came next. This started with 50mg daily and up-titration options in increments of 25 mg every two weeks up to a maximum of 100 mg and down-titration anytime to a min of 50 mg. The sponsor enrolled 134 adult subjects with hypoparathyroidism with a 2:1 randomization of treatment to placebo in 29 investigative sites. Of the 134 eligible subjects, 90 were randomized to NPS558 and 44 to placebo. All 134 were included in the Intent-to-Treat (ITT) and safety analyses and 115 were included in the Per Protocol (PP) analysis. Thirteen subjects discontinued prior to the end of treatment. Of the six in the treatment arm, three were due to AEs, one unspecified subject decision, one lost to follow-up and one investigator decision. In the control group there were seven who discontinued: three were investigator's decision due to noncompliance with study procedures, three were personal decisions, and one was due to unspecified noncompliance. Ten additional subjects were also excluded in this review due to multiple GCP violations in the clinical site from which they received treatments.

3.1.1 Primary Endpoint

The primary efficacy endpoint in the main CL1-11-040 study was the percentage of responders at Week 24, based on investigator-prescribed data relating to a composite endpoint of three components,

1. At least a 50% reduction from the baseline oral calcium dose
2. At least a 50% reduction from the baseline active vitamin D dose. It should be noted that adjustments were made to the baseline doses so the two different types of vitamin D (calcitriol and alphacalcidol) administered in the study would be equivalent (2 doses of alphacalcido = 1 dose of calcitriol)
3. An albumin corrected total serum calcium concentration that was maintained or normalized compared to the baseline value ($\geq$7.5 mg/dL) and did not exceed the upper limit of the laboratory normal range.

The primary efficacy endpoint occurred at week 24. If an ITT subject dropped out early or didn't have assessments at Week 24, then the last efficacy assessments were carried forward (LOCF). Subjects were considered non-responders if they did not have sufficient drug exposure (discontinued treatment before Visit 14 (Week 16)). If a subject was enrolled before protocol amendment 7.0 then the primary endpoint was subject to slight modifications regarding the albumin corrected total serum calcium concentration. These differences, however, made little difference in the results for pre and post-amendment 7 results with one subject in the RhPTH(1-84) group that would have been considered a responder had she come in after amendment 7.0, but was considered a non-responder due to her entry under amendment 4.

The primary analysis was conducted using all randomized subjects receiving at least one dose and having at least one post-baseline efficacy measurement. The 2-sided Fisher's Exact test was used to test for responder rate difference between RhPTH(1-84) and placebo.

The primary endpoint for all 3 NPS sponsored efficacy studies supporting the main study were also similar composites as shown below in the applicant generated table below (Table 4).

Table 4: Applicant's Table of Composite Endpoints for NPS Sponsored Efficacy Studies

Study	CL1-11-040	PAR-C10-007	PAR-C10-008	PAR-C10-009
Duration at Endpoint	**24 weeks**	**8 weeks**	**52 weeks**	**24 weeks**
Response Criteria[a]				
Oral Calcium	≥ 50% reduction from baseline	Reduction to ≤ 500 mg/day	≥ 50% reduction from baseline **OR** Dose of ≤ 500 mg	≥ 50% reduction from baseline **OR** Dose of ≤ 500 mg
Calcitriol/Alphacalcidol	≥ 50% reduction from baseline	Reduction to ≤ 0.25 µg/day (calcitriol)	≥ 50% reduction from baseline **OR** Dose of ≤ 0.25 µg/day (calcitriol)	≥ 50% reduction from baseline **OR** Dose of ≤ 0.25 µg/day (calcitriol) or ≤ 0.50 µg/day (alphacalcidol)
Serum ACSC[b]	Maintained or normalized compared to baseline value (≥ 7.5 mg/dL) and did not exceed the laboratory ULN	Between 7.5 mg/dL and the ULN for the central laboratory	Between 7.5 mg/dL and the ULN for the central laboratory	Normalized or maintained compared to the baseline value and did not exceed the ULN of the central laboratory

ACSC = albumin-corrected total serum calcium concentration; ITT = Intent-to-treat; ULN = upper limit of normal
In order to meet the definition of a responder, all 3 criteria had to be met at the same time.
[a] Response criteria was based on ITT population using investigator-prescribed dosing data.
[b] Total serum calcium was response criterion for Study PAR-C10-009
Source: Table 4-7 in the Integrated Summary of Efficacy report

3.1.2 Secondary Endpoints

A fixed sequence testing procedure was used to control the Type I Error. If the primary endpoint was found to be significant then the first secondary endpoint was tested. Secondary efficacy endpoints are (provided in the testing sequence):

1. Percent change from baseline in calcium supplementation dose at Visit 16 (Week 24) in the NPSP 558 treatment group vs. placebo.
2. Proportion of subjects that achieve independence from supplemental active vitamin D metabolite/analog usage AND a calcium supplementation dose of 500 mg/day, or less by Visit 16 (Week 24) in the NPSP 558 treatment group vs. placebo.
3. The frequency of clinical symptoms of hypocalcemia (including paresthesiae, muscle cramping, tetany, seizures) during Visit 14 (Weeks 16) to visit 16 (Week 24) in the NPSP 558 treatment group vs. placebo.

In order to create a response rate for the third secondary endpoint, I used the sponsor list of adverse event preferred terms for hypocalcemia symptoms. The AEs listed for 'hypcocalcemia' and 'hypocalcemia symptoms' were used in my calculations which provided different rates, but these were found to be equally non-significant.

3.2 Statistical Methodologies

I ran a worst comparison scenario sensitivity analysis for all primary and key secondary endpoints wherein all non-completers were considered responders if they were under placebo and non-responders under RhPTH(1-84). For secondary endpoints measuring change from

baseline, the highest level of supplementation observed over the course of the study was imputed for those in the RhPTH(1-84) arm and the lowest level for those under placebo.

3.3 Results and Conclusions

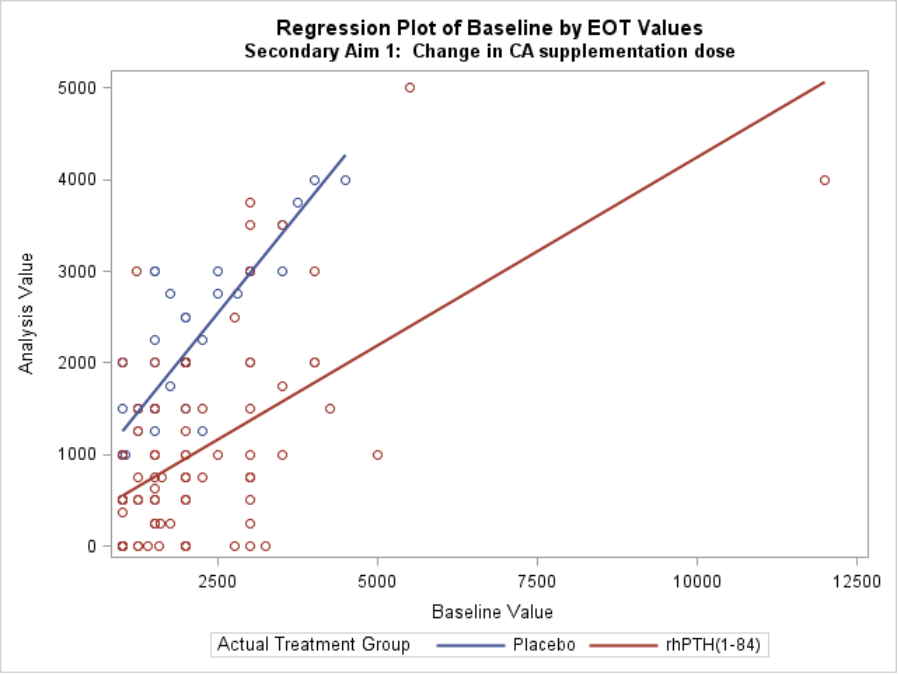
For the primary analysis, a statistically significant difference ($p<0.0001$) was found for responder rates in the ITT population when comparing treatment (54.8%) to placebo (2.5%). There were a total of 44 responders that were recorded at week 24 and two responders which were imputed by the applicant using a LOCF method. A worst comparison scenario imputation analysis was also run wherein all those with missing endpoints in the RhPTH(1-84) arm were imputed as non-responders and those in the placebo arm were imputed as responders. Results also remained significant across the worst comparison scenario indicating that these results will remain statistically significant under other less stringent imputation methods with this particular endpoint. Due to a concern on what may be considered stable for serum calcium, an analysis was also performed based on the endpoint revisions described in section 1.2, Statistical Issues and Concerns. Under this scenario there were a total of 26 observed responders at week 24 and one responder imputed using LOCF to create a total of 27 responders in the RhPTH(1-84) treatment arm. Although there was a substantial drop in the response rate with this new endpoint, it remained statistically significant showing a difference in response rate from placebo. Results for the primary endpoint were calculated using the modified dataset (MDS) which removes the site with multiple GCP violations described in Section 1.2. Table 5, given below, shows results using the LOCF method, the worst comparison scenario imputation for non-completers, and the revised serum calcium primary endpoint for the MDS.

Table 5: Primary Endpoint Analysis Results

		Placebo (N=40)		RhPTH(1-84) (N=84)		Treatment Difference	
		n (%)	Exact 95% CI	n (%)	Exact 95% CI		P
Primary Analysis	Non-Responder	39 (97.5)	(0.1, 13.2)	38 (45.2)	(43.5, 65.7)	52.3 (40.6, 64)	<.0001
	Responder	1 (2.5)		46 (54.8)			
Worst Comparison	Non-Responder	31 (77.5)	(10.8, 38.5)	40 (47.6)	(41.2, 63.4)	29.9 (13.1, 46.7)	0.0019
	Responder	9 (22.5)		44 (52.4)			
Changing Serum CA (8-9)	Non-Responder	39 (97.5)	(0.1, 13.2)	57 (67.9)	(22.4, 43.2)	29.6 (18.6, 40.7)	<.0001
	Responder	1 (2.5)		27 (32.1)			

Since the primary endpoint was significant it was appropriate to proceed with testing procedures for the secondary endpoints. The first secondary endpoint indicated a statistically significant reduction ($p<0.001$) from baseline in supplemental calcium dose for the RhPTH(1-84) group (51.8% mean reduction), when compared with placebo (-6.56%). Figure 2 shows a scatter plot of the calcium supplementation at baseline and at end of treatment with regression lines drawn for each treatment arm.

Figure 2: Calcium Supplementation at Baseline and End of Treatment



The next secondary endpoint shows a statistically significant difference ($p<.0001$) in response between RhPTH(1-84) and placebo for the proportion of subjects (41.67% vs. 2.5%) who achieved independence from supplemental active vitamin D and reduced their calcium supplementation dose to ≤500 mg daily.

For the last secondary endpoint, which concerned safety on the frequency of clinical symptoms of hypocalcemia during Visit 14 (Weeks 16) to visit 16 (Week 24), I used a table submitted by the applicant detailing symptoms of hypocalcemia. This led to slightly different response rates from those given by the applicant. Table 11-7 in the clinical study report listed 30/90 (33.3%) subjects in the Natpara arm and 18/44 (40.9%) of subjects on placebo with symptoms of hypocalcemia during this time period. This led to non-significant findings ($p=0.39$) when testing for a difference between the two arms. In running this endpoint, I found a non-significant difference ($p=0.69$) between the proportion of subjects exhibiting symptoms of hypocalcemia with RhPTH(1-84) (35.7%) when compared with placebo (30%).

Results for all key secondary endpoints are shown in Table 6 using both the LOCF methodology. Statistical significance remains robust to the applied imputation methodology.

Table 6: Results for Key Secondary Endpoints

	Placebo (N_{MDS}=40)	RhPTH(1-84) (N_{MDS}=84)	Difference in Means/OR* (95% CI)	P**
Endpoint 1: Percent Change from Baseline in CA Supplementation				
CA Reduction ≥ 50%, n(%)	3 (7.5)	58 (69.1)	27.5(7.8, 97.4)	<.0001
% Reduction from Baseline CA, Mean (SD)	-6.56 (38.5)	51.80 (44.6)	58 (41.8, 74.2)	<.0001
Absolute Reduction from Baseline CA, Mean (SD)	-85 (536.3)	1152 (1219)	1135.8 (838.6, 1433)	<.0001
Endpoint 2: Independence from Supplemental Active Vitamin D metabolite/analog and CA supplementation dose ≤ 500 mg/day by Week 24				
Achieved Secondary Endpoint 2	1 (2.5)	35 (41.7)	27.9 (3.7, 212.5)	<.0001
Endpoint 3: Frequency of Hypocalcemia symptoms between Weeks 16 and 24 (Comparing proportions with symptoms)				
	12 (30)	30 (35.7)	1.3 (0.6, 2.9)	0.6851

*Odds Ratio calculated for binary variables, differences and CI calculated for continuous based on ANCOVA model

**P-values based on Fisher's Exact test for binary variables, and ANCOVA adjusting for baseline with continuous variables

3.3.1 Serum Calcium Levels Over Time

Figure 3 below shows the mean serum calcium levels for each arm over the course of the treatment period. However, since the clinical interest is to have patients within the normal range rather than at higher or lower level, Figure 4, which shows the proportion of subjects with low, normal, or high serum calcium levels, may be of more use in gaining better insight on how patients performed in each arm. Due to the low proportion of subjects that had a higher serum calcium level, that plot is on a different scale (0%-5%) from plots with low or normal serum calcium levels (0%-80%). Table 7 gives the actual numbers and percentage of patients in each group for each visit.

Figure 3: Mean Serum Calcium over Time

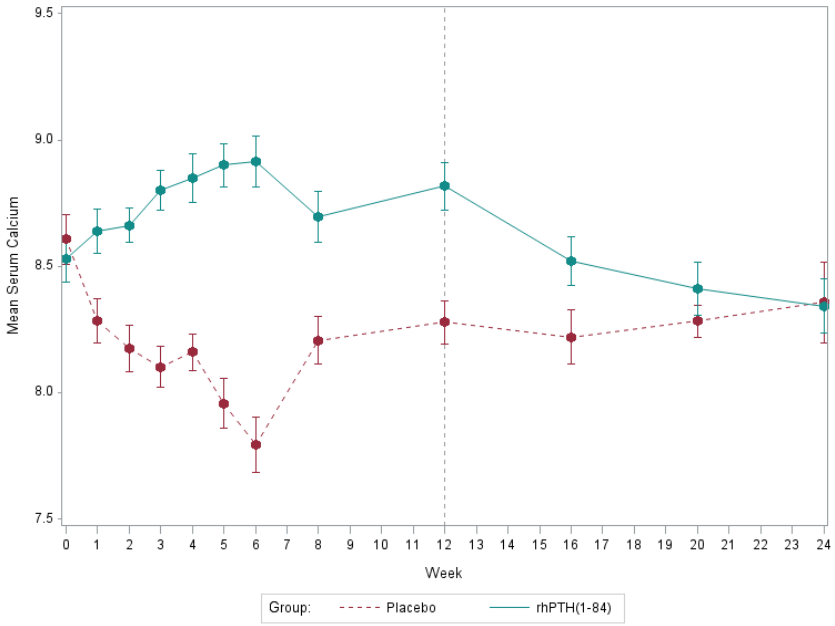


Figure 4: Percentage of Subjects with Low, Normal, and High Serum Calcium Levels over Time

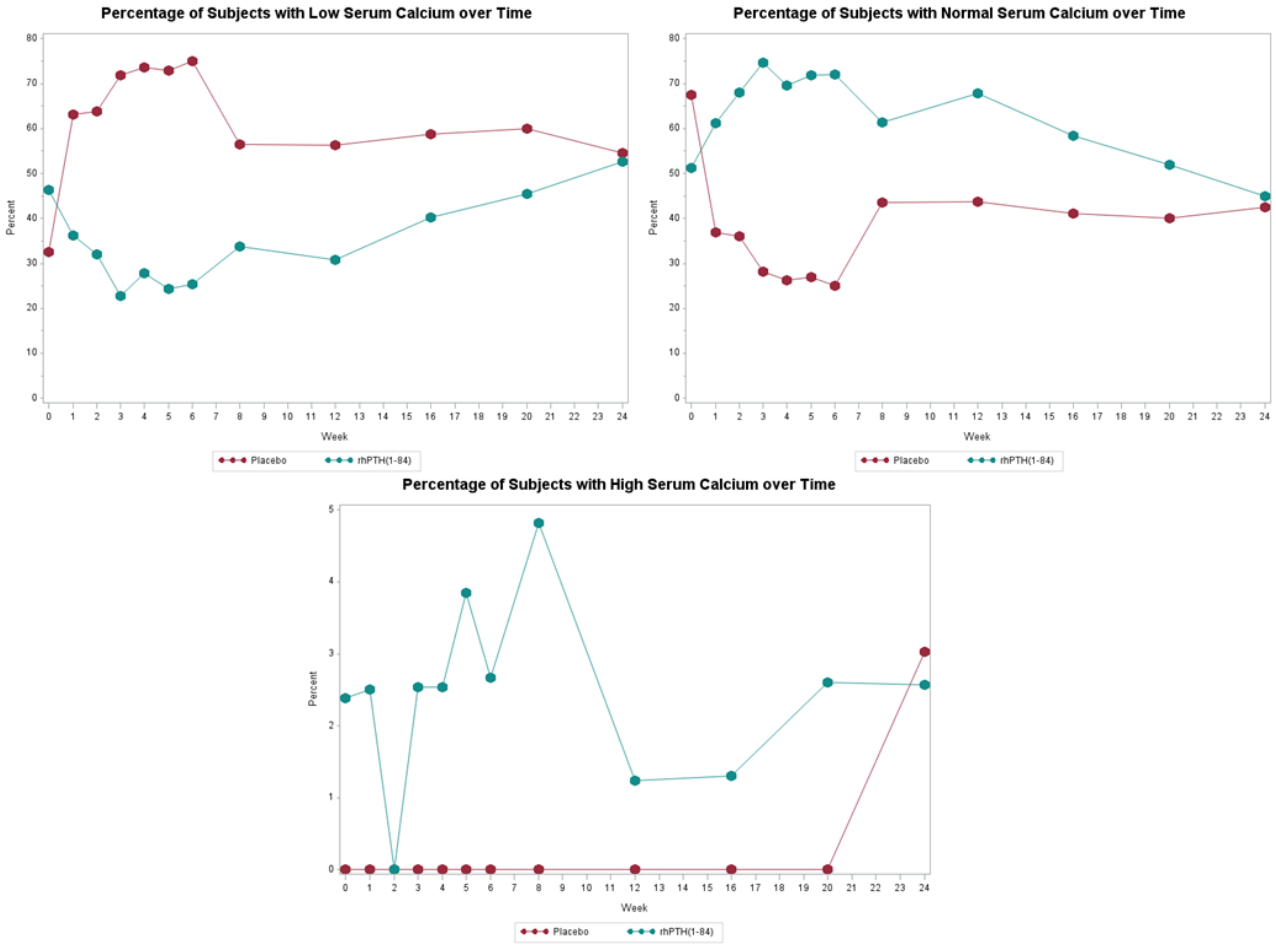


Table 7: Serum Calcium Levels over Time

	Serum CA Levels	Placebo n (%)	rhPTH(1-84) n (%)
Baseline	**<8.4**	13 (32.5%)	39 (46.4%)
	8.4 to 10.6	27 (67.5%)	43 (51.2%)
	≥10.6	0 (0%)	2 (2.4%)
Week 1	**<8.4**	24 (63.2%)	29 (36.3%)
	8.4 to 10.6	14 (36.8%)	49 (61.3%)
	≥10.6	0 (0%)	2 (2.5%)
Week 2	**<8.4**	23 (63.9%)	24 (32%)
	8.4 to 10.6	13 (36.1%)	51 (68%)
	≥10.6	0 (0%)	0 (0%)

Week 3	**<8.4**	28 (71.8%)	18 (22.8%)
	8.4 to 10.6	11 (28.2%)	59 (74.7%)
	≥10.6	0 (0%)	2 (2.5%)
Week 4	**<8.4**	28 (73.7%)	22 (27.9%)
	8.4 to 10.6	10 (26.3%)	55 (69.6%)
	≥10.6	0 (0%)	2 (2.5%)
Week 5	**<8.4**	27 (73%)	19 (24.4%)
	8.4 to 10.6	10 (27%)	56 (71.8%)
	≥10.6	0 (0%)	3 (3.9%)
Week 6	**<8.4**	27 (75%)	19 (25.3%)
	8.4 to 10.6	9 (25%)	54 (72%)
	≥10.6	0 (0%)	2 (2.7%)
Week 8	**<8.4**	22 (56.4%)	28 (33.7%)
	8.4 to 10.6	17 (14.6%)	51 (61.5%)
	≥10.6	0 (0%)	4 (4.8%)
Week 12	**<8.4**	18 (56.3%)	25 (30.9%)
	8.4 to 10.6	14 (43.8%)	55 (67.9%)
	≥10.6	0 (0%)	1 (1.2%)
Week 16	**<8.4**	20 (58.8%)	31 (40.3%)
	8.4 to 10.6	14 (41.2%)	45 (58.4%)
	≥10.6	0 (0%)	1 (1.3%)
Week 20	**<8.4**	18 (60%)	35 (45.5%)
	8.4 to 10.6	12 (40%)	40 (52%)
	≥10.6	0 (0%)	2 (2.6%)
At or above Week 24	**<8.4**	18 (54.6%)	41 (52.6%)
	8.4 to 10.6	14 (42.4%)	35 (44.9%)
	≥10.6	1 (3%)	2 (2.6%)

3.3.2 Calcium Intake over Time

Having a reduction in calcium intake is a clinically important aim in this treatment. Thus, it was included as both a part of the composite endpoint and also as a secondary endpoint. This section gives a broader view of calcium intake over the course of the treatment period. Figure 5 illustrates the median amount of calcium intake along with the interquartile range for each treatment arm. A similar pattern over time is also seen in Figure 6 with the differences from baseline in calcium intake at each visit.

Figure 5: Median Calcium Intake over Time

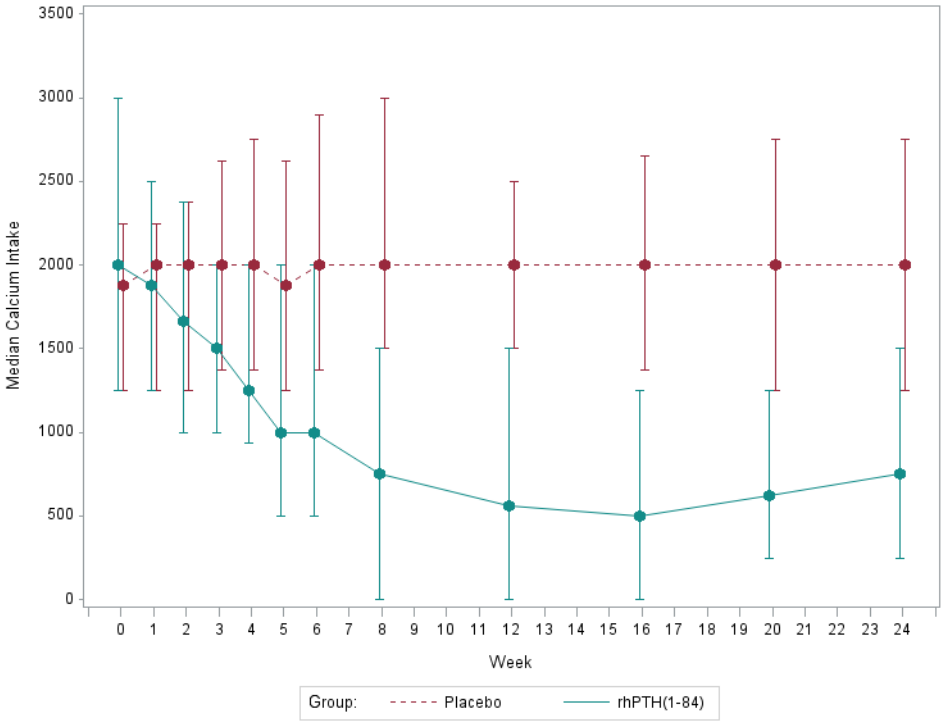
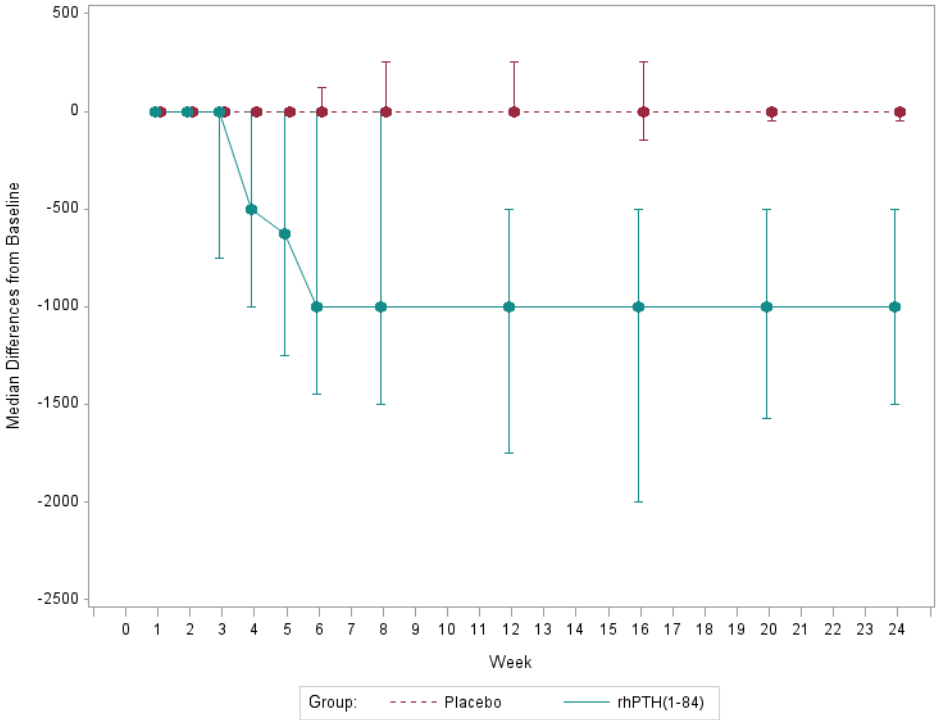


Figure 6: Median Difference from Baseline Calcium over Time



3.3.3 Vitamin D Intake over Time

Part of the composite endpoint and one of the secondary endpoints involved vitamin D intake and independence from vitamin D. This section shows vitamin D intake results as a single endpoint rather than as a composite as is seen in previous sections. The difference from baseline in vitamin D intake was found for both arms and the median along with the interquartile range is shown over time in Figure 7. Since having patients that do not need any vitamin D supplements is clinically relevant, Figure 8 shows the percentage of patients in each arm who achieve this at each visit during the treatment period.

Figure 7: Median Difference from Baseline in Vitamin D Intake over Time

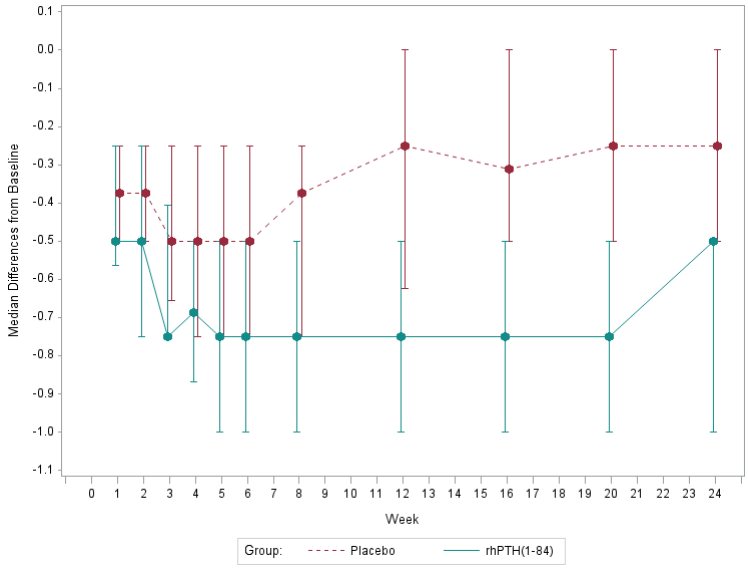
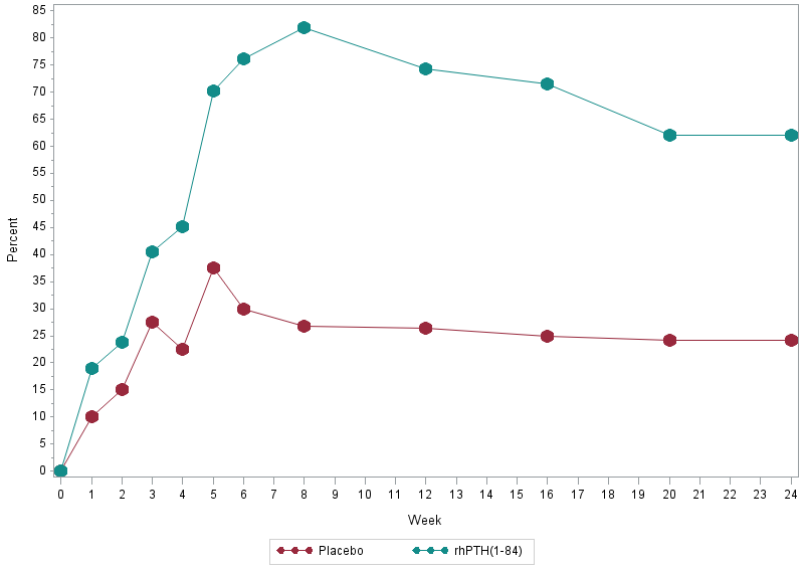


Figure 8: Percent of Patients with no Vitamin D Intake



4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses done for the primary efficacy endpoint were pre-specified by the applicant. The baseline intrinsic factors considered for analysis were:

- Age (<65)
- Gender
- Geographic Region (North America)
  (North America includes Canada and the United States. Other countries in the study include: France, Italy, Belgium, Denmark, the United Kingdom, and Hungary.)

The disease-related factors specified for subgroup analyses were:

- Prescribed active vitamin D metabolite/analog at baseline (high dose, medium dose, and low dose. For calcitriol: low Dose 0-0.25 μg/day, medium dose >0.25-0.5 μg/day, high dose >0.5 μg/day; for alphacalcidol: low dose 0-0.50 μg/day, medium dose >0.50-1.0 μg/day, high dose >1.0 μg/day)
- Prescribed calcium at baseline (0-2000 mg/day, >2000 mg/day)
- Duration of hypoparathyroidism (≤5 years, >5-10 years, >10 years)

Testing for subgroups based on race was not pre-specified in the protocol, but was included in this review. Since the overall subject population in the FAS was predominantly white (96%), this was analyzed as a binary variable with subjects in the 'other' category including those of black, Asian, and Hawaiian/Pacific Islander descent.

As there was only one response in the placebo group, tests for interaction effects were not performed.

4.1 Subgroup Results

Results for the primary endpoint in each subgroup are shown in Table 8 below. In general, the subgroup analysis results remained consistent with the overall efficacy results presented in Section 3.3.

Table 8: Proportion of Responders within Subgroups

		Placebo (N=40)	RhPTH(1-84) (N=84)
		n (%)	n (%)
Age	<65 Years	1/36 (2.8%)	42/80 (52.5%)
	≥65 Year	0/4 (0%)	4/4 (100%)
Gender	Male	0/7 (0%)	10/19 (52.6%)
	Female	1/33 (3%)	36/65 (55.38%)
Baseline Active Vitamin D	Low Dose	1/3 (33.3%)	5/6 (83.3%)
	Medium Dose	0/12 (0%)	11/22 (50%)
	High Dose	0/25 (0%)	30/56 (53.6%)

Calcium Supplementation at Baseline	**Baseline CA ≤ 2000 mg**	1/29 (3.5%)	35/57 (61.4%)
	Baseline CA > 2000 mg	0/11 (0%)	11/27 (40.7%)
Duration of Hypoparathyroidism	**≤ 5 Years**	1/10 (10%)	12/25 (80%)
	5-10 Years	0/13 (0%)	17/27 (63%)
	>10 Years	0/17 (0%)	17/42 (40.5%)
Geographic Region	**North America**	1/21 (4.8%)	26/43 (60.5%)
	Europe	0/19 (0%)	20/41 (48.8%)
Race	**White**	1/39 (2.6%)	45/80 (56.3%)
	Other	0/1 (0%)	1/4 (25%)

5 SUMMARY

5.1 Statistical Issues

One clinical site which accounts for almost 8% of the data was excluded from the analysis due to multiple GCP violations. Various imputation methods and exclusion tactics have been implemented in this review to see how well the findings stand up to missing data problems and known protocol violations. However, if there is an underlying flaw in the methodology or clinical practices used when collecting the data used for the analysis, then the findings presented here will reflect these biases and may not be indicative of what would happen in a real-world setting.

5.2 Collective Evidence

A substantial issue has to do with the primary efficacy endpoint and how the sponsor defined *normal* for serum calcium levels. After recalculating this endpoint based on new criteria (see Section 1.2) I found a much lower response rate for those being treated with RhPTH(1-84), the response dropping from 55% to 32%. However, the difference when compared to the placebo arm under this new definition remained statistically significant. Secondary endpoints for reduction in calcium supplementation and independence from supplemental active vitamin D and calcium were also statistically significant.

CLINICAL PHARMACOLOGY ASSESSMENT: ADEQUACY OF NATPARA DOSAGE REGIMEN IN TREATMENT OF HYPOPARATHYROIDISM

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List of Figures and Tables

1 Executive Summary

Adequacy of the proposed dosage regimen of Natpara:

The sponsor has proposed that Natpara (also referred to as rhPTH[1-84] in this document) is intended for once daily (QD) administration by subcutaneous (SC) injection. The injection site is alternated between each thigh. Sponsor proposes a starting dose of 50 µg QD, which can be titrated at approximately 2- to 4-week intervals upward to doses of 75 µg and then 100 µg QD based on serum calcium response. Downward titration to a minimum dose of 25 µg QD can occur at any time.

Based on the data submitted in the BLA, it is evident that when compared to the placebo group receiving standard care (combination of stable oral calcium and vitamin D dose), the proposed once daily dosage regimen for Natpara was adequate in reducing the calcium and vitamin D dose requirement while maintaining the mean albumin corrected total serum calcium within the 8-9 mg/dL target, albeit closer to the upper target limit. However, the once daily dosing regimen proposed by the sponsor is not adequate to control hypercalciuria (24-hour urinary calcium >300 mg/day for males or >250 mg/day for females).

It is important to note that in this program no dose ranging studies were conducted for dose or dosing regimen selection of Natpara in patients with hypoparathyroidism before proceeding to the registration trial. Furthermore, pharmacokinetic and pharmacodynamic (PKPD) studies were conducted while the Phase 3 trials were ongoing. PKPD data revealed that dosing regimen of Natpara up to 100 µg do not provide optimal systemic exposures over the entire duration of a day to control the excretion of calcium in urine. This is primarily due to short half-life (~ 3 hours) of Natpara, which results in PTH concentrations returning to baseline by 10-12 hours. In addition, the peak concentrations of PTH (~230 pg/mL) far exceed the observed normal physiological range of PTH (10-65 pg/mL). The sponsor acknowledged that PTH effects on serum calcium are driven by the duration of exposure rather than magnitude as demonstrated by the data. FDA clinical pharmacology reviewers are of the opinion that the duration of Natpara induced reduction in urinary calcium excretion is not long enough to control the excretion of calcium regardless of whether patients achieve normocalcemia. Although, we acknowledge that it could also be an artifact of saturation of the renal active transport system by the increased filtered load of calcium, triggered by the PTH effect in the first-half of the 0-24 hour duration.

To evaluate the adequacy of the dosage regimen (QD vs. a more frequent vs. slow release profile by formulation change) in balancing serum calcium and hypercalciuria, mechanistic evaluation methodology was used. Considering the complex nature of calcium homeostasis, a systems pharmacology model of calcium homeostasis[1] was utilized to understand the effect of changing the Natpara dosing regimen or hypothetically altering the formulation release profile on serum and urine calcium profiles. The systems pharmacology model was able to describe the time course of PTH, calcitriol, serum calcium, and 24-hour urinary calcium excretion after placebo or rhPTH

[1] A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. Mark C. Peterson and Matthew M. Riggs. Bone 46 (2010) 49–63.

treatment from the single and multiple QD dose PKPD trial. Thus, providing confidence that the model could be used to project PTH and serum calcium profiles for dosing scenarios, which were not evaluated in the clinical trials. The simulations demonstrate that conceptually, PTH hormone replacement therapy demands for exposures closer to physiological profile. A comparison of the model projected serum calcium and 24-hour urinary calcium excretion data, obtained by evaluating various scenarios, demonstrate that it is feasible to achieve control on both serum calcium and 24-hour urinary calcium excretion with a lower and more frequent dosage regimen than QD or a QD dosing regimen with a slow release formulation. As an example, for a typical hypoparathyroidism patient with 50% loss in PTH gland pool and a background daily intake of 2000 mg Ca and 1.5 µg Vitamin-D, the 24 hour urinary calcium without PTH treatment was projected to be 18.8 mmol/day, which was projected to decrease to 10.8, 8.5, and 7.5 mmol/day (still >ULN) with 100 µg QD, 50 µg BID and 50 µg QD with slow release profile rhPTH treatments, respectively. For a different scenario, assuming a typical patient with ~ 99% loss in PTH gland pool and a background daily intake of 2000 mg Ca and 1.5 µg Vitamin-D, the 24 hour urinary calcium without PTH treatment was projected to be 32.8 mmol/day, which was projected to decrease to 13.4, 7.8, and 7.5 mmol/day (still >ULN) with 100 µg QD, 50 µg BID and 100 µg QD with slow release profile rhPTH treatments, respectively. It is worth noting that these projections are for a typical patient without incorporating the PKPD variability and titration scenarios. Further projections by incorporating variability and titrations will be needed to completely understand the impact of altering the dosing regimen or the formulation release profile on serum and urinary calcium profile. Nevertheless, the simulation results demonstrate that in principle the change in dosing regimen or alteration of the formulation release profile will be beneficial in reducing 24-hour urinary calcium while maintaining normocalcemia.

Furthermore, these results are consistent with the PKPD profile of Natpara described later in detail that demonstrates that a once daily regimen of Natpara does not provide optimum duration of pharmacological action which may have also resulted in lack of benefit in terms of reducing urine calcium in the registration trial. These projections are also consistent with the published literature, which suggests that more frequent administration[2] or slow SC infusion[3] delivery of rhPTH (1-34), a related peptide, was able to achieve control on calcium and urinary calcium excretion at roughly half the daily dose.

The FDA clinical pharmacology reviewers believe that adequate understanding of the reasons behind hypercalciuria and possible mitigation of this safety concern is essential for Natpara. Hypercalciuria is one of the primary safety concerns for the conventional therapy that results from using higher than usual calcium and vitamin-D doses. In general population, the relative risk of nephrolithiasis exponentially increases above a urinary calcium excretion of ~200-300 mg/day[4,13]. Furthermore, acknowledging that there are no formal guidelines for the therapy, medical literature recognizes the long term goals for the therapy in patients with hypoparathyroidism as: "*symptom control, a serum albumin-*

[2] Karen K. WINER et al. J Clin Endocrinol Metab 83: 3480–3486, 1998.

[3] Karen K. Winer et al. J Clin Endocrinol Metab 97: 391–399, 2012.

[4] Andrew F. Stewart and Arthur E. Broadus. The Regulation of Renal Calcium Excretion: An Approach to Hypercalciuria. Ann. Rev. Med. (1981) 32: 457-73

corrected total calcium level at the lower end of the normal range (approximately 8.0 to 8.5 mg per deciliter [2.00 to 2.12 mmol per liter]), a 24-hour urinary calcium level well below 300 mg, and a calcium–phosphate product below 55. Higher products can lead to precipitation of calcium–phosphate salts in soft tissues (e.g., kidney, lens, and basal ganglia)"[5]. Overall, based on the review of PK/PD profile of Natpara, efficacy/safety results from the registration trial, and mechanistic evaluations conducted using a calcium homeostasis model; it is evident that a lower and more frequent dosing regimen than QD or a QD dosing regimen with a slow release formulation will likely provide a better control on hypercalciuria. Therefore, the dose regimen should be further optimized to address the safety concerns for hypercalciuria.

PKPD of Natpara in patients with Hypoparathyroidism:

The PKPD of Natpara was assessed from two clinical pharmacology studies that evaluated Natpara PK/PD in patients with hypoparathyroidism.

Overall, PKPD data from short-term and long-term SC administration of rhPTH[1-84] at 100 µg dose in the thigh, as assessed by serum and urinary PD markers, revealed that:

- rhPTH[1-84] administration results in a dose-dependent increase in plasma PTH levels, which at peak far exceeded the observed normal physiological range of PTH (10-65 pg/mL). There was also a dose-dependent rise in serum calcium. This rise in serum calcium seems to be orchestrated by PTH effect on urinary calcium excretion (via cAMP activation) and gut absorption (via calcitriol increase).
- Natpara induced reduction in urinary calcium excretion (i.e. stimulatory action of Natpara on calcium re-absorption) is short-lived (10-12 hours) with single or multiple doses of up to 100 µg. This is primarily due to short half-life (~ 3 hours) of Natpara, which results in PTH concentrations returning to baseline by 10-12 hours. The PTH effects on serum calcium are driven by the duration of exposure rather than magnitude as demonstrated by the data.

Natpara efficacy/safety results:

In the registration trial CL1-11-040, when compared to the placebo group receiving standard care (combination of stable oral calcium and vitamin D dose), the proposed dosing regimen for Natpara was adequate in reducing the calcium and vitamin D dose requirement (mean decrease of about 52% and 77%, respectively, from baseline (mean calcium and vitamin D doses of 2160 mg and 0.9 µg, respectively), while maintaining the albumin corrected total serum calcium within the 8-9 mg/dL target, albeit closer to the upper target limit. For more details on the efficacy, please refer to Clinical Section of the FDA EMDAC briefing document.

In addition, at each visit there was substantial proportion of patients with 24-hour urinary calcium values (>50%) above the upper limit of normal (ULN) with Natpara treatment than placebo. As discussed in the Clinical Section of the FDA EMDAC briefing document, from a safety perspective, mean 24-hour urinary calcium excretion remained above the ULN (300 mg/day) with the rhPTH[1-84] treatment while for placebo (standard of care, Ca/Vit D), mean 24-hour urinary calcium excretion remained within the normal range 50-300 mg/day). Hypercalciuria is one of the primary safety concerns

[5] Dolores Shoback, M.D. Hypoparathyroidism. N Engl J Med. (2008) 359:391-403

with current standard of care (nephrolithiasis, soft tissue calcification, end organ damage) and thus an expectation from Natpara as a hormone replacement therapy, is that it provides additional benefit in terms of reducing urinary calcium excretion.

2 Clinical Pharmacology Perspective on Natpara PKPD

2.1 Recapitulation of key mechanistic and physiological aspects of parathyroid hormones that are relevant to Natpara

Natpara® (rhPTH[1-84]) for injection is a replacement for endogenous parathyroid hormone, indicated for the long-term treatment of Hypoparathyroidism.

Hypoparathyroidism is a rare endocrine deficiency that is characterized by absent or inappropriately low circulating parathyroid hormone (PTH) levels, in association with hypocalcemia, hyperphosphatemia, and hypercalciuria.

Parathyroid hormone (PTH), which is secreted by the parathyroid glands, has a variety of important physiological functions (see **Figure 1**) as illustrated below:

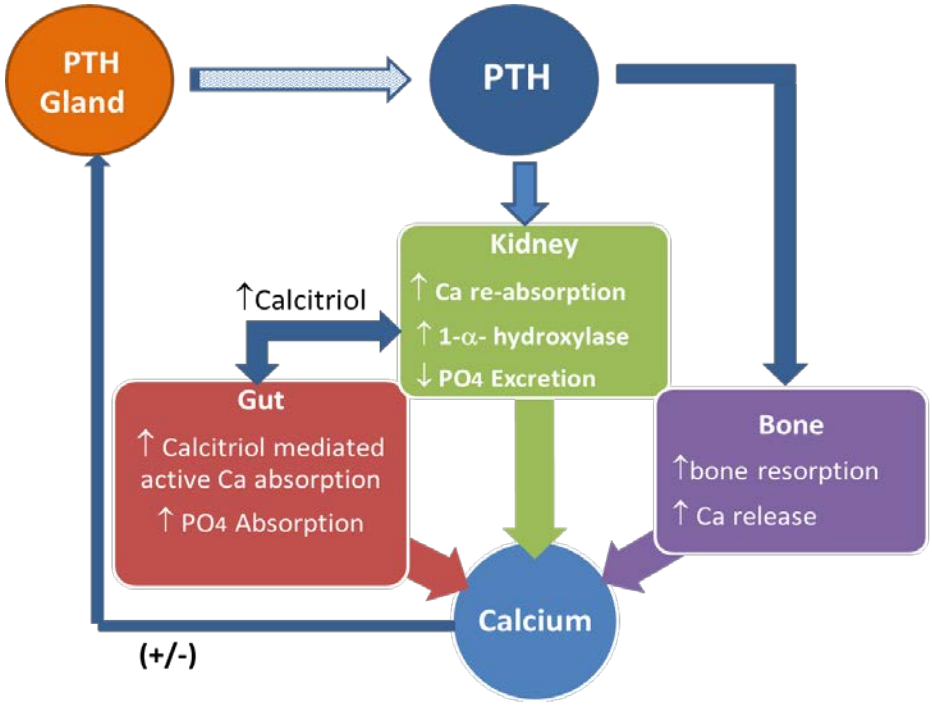


Figure 1 Parathyroid Hormone Mechanism of Action

- PTH regulates bone metabolism and serum levels of calcium and phosphate: when serum calcium is low, the parathyroid glands increase PTH secretion, when the serum calcium is high, the PTH secretion is reduced. The parathyroid glands sense the level of extracellular calcium at the surface of the parathyroid cell and adjust the synthesis and secretion of PTH accordingly. The relationship between ionized extracellular calcium and PTH secretion is steep curve where small variations in calcium level lead to significant changes in PTH secretion.
- In kidney, PTH stimulates calcium reabsorption at the proximal tubule and excretion at the distal nephron. The overall effect of increased PTH is reduced urinary calcium excretion. In addition, PTH stimulates the 25(OH)D_3-1-α-hydroxylase that converts

25(OH) vitamin D into 1,25-dihydroxyvitamin D [1,25$(OH)_2$ vitamin D; calcitriol]. This active metabolite of vitamin D facilitates the absorption of calcium and phosphate from the intestine.

- In bone, PTH regulates the vast skeletal reservoir of calcium which amounts to 99% of total body calcium. This regulation occurs by effects on bone turnover (the process of bone formation and bone resorption known as bone remodeling).
- The net effect of increasing PTH levels is to increase serum calcium, reduce urinary calcium excretion, increase urinary phosphorus excretion, and reduce the serum phosphate level.
- In healthy subjects, the normal negative feedback mechanism is provided by the rise in serum calcium that inhibits PTH secretion, and in both healthy and patients with hypoparathyroidism, the increase in 1,25$(OH)_2$ vitamin D that limits the activation by PTH on the 1-α-hydroxylase.

To understand the clinical consequences of Natpara exposure to human biological system, another key aspect is the calcium homeostasis from a mass balance perspective and role of PTH hormone in it. Figure 2 illustrates the day to day mass balance of calcium[6,7] in a typical adult.

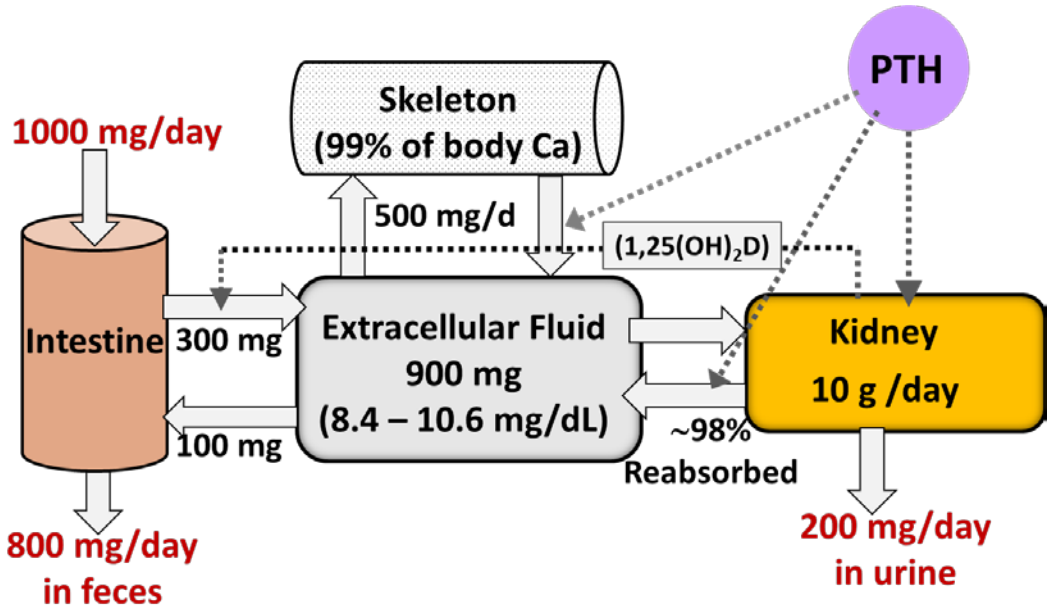


Figure 2 Mass balance of calcium homeostasis: Regulation of calcium excretion by parathyroid hormone is one the key factor in defining the net influx and outflow of calcium and plays critical role in maintaining normocalcemia and normocalciuria

Kidney reacts quickly to PTH changes, where PTH exerts a direct action on distal nephron to decrease calcium excretion. In healthy individuals, on a daily basis 10 g of

[6] Adapted from: G A Clines and T A Guise. Endocrine-Related Cancer. (2005) 12: 549–583 and
[7] Chapter 43. Hormonal Regulation of Calcium Metabolism. H.M. Goodman in Essential Medical Physiology. Edited by – LR Johnson and JH Lyme

calcium is filtered and ~90% of filtered calcium load is passively reabsorbed independent of PTH. PTH provides the fine tuning of calcium excretion in urine by controlling the active re-absorption of remaining calcium. This active transport process is biologically designed to be of low capacity and saturates at high filtered load (to prevent hypercalcemia). Considering the high filtered load of calcium, even small changes in fraction absorbed have potential to cause dramatic changes in amount of calcium excreted in urine. For this reason, patients with hypoparathyroidism with calcium in normal range generally excrete 3-fold higher calcium in absence of/low levels of PTH.

Physiological PTH secretion follows a diurnal pattern,[8,9] which is considered to be important in regulation of calcium homeostasis especially, for exerting a tight control on the urinary excretion pattern of calcium (See **Figure 3** below).

Circadian rhythm in PTH and Urinary Ca Excretion profiles: Temporal pattern for the UCa/Cr curve is a mirror image of the PTH curve

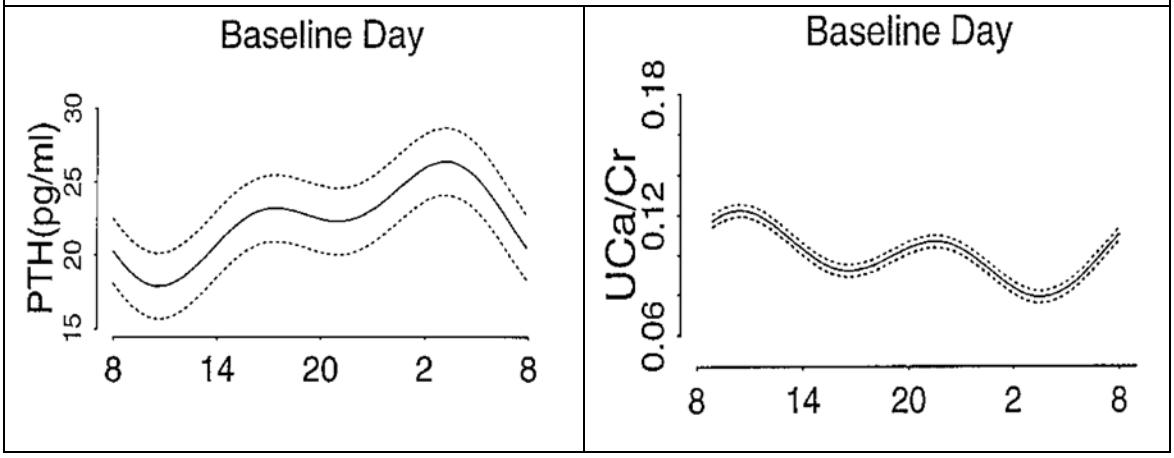


Figure 3 Circadian rhythm of endogenous PTH, serum and urinary calcium [Mean (±2SD) in11 healthy men]

2.2 Pharmacokinetic and pharmacodynamic characteristics of Natpara after SC administration in patients with hypoparathyroidism and relation to the dose

Overall, PKPD data from short-term and long-term SC administration of Natpara at 100 µg dose in the thigh, as assessed by serum and urinary PD markers, revealed the following:

- Natpara administration results in a dose-dependent increase in plasma PTH exposure. There was also a dose-dependent increase in serum calcium. This rise in serum calcium seems to be orchestrated by Natpara effect on urinary calcium excretion (via cAMP activation) and gut calcium absorption (via calcitriol increase). However, discrete assessments of serum and urinary markers have

[8] Circadian rhythm in serum parathyroid hormone concentration in human subjects: correlation with serum calcium, phosphate, albumin, and growth hormone levels. W Jubiz, JM Canterbury, E Reiss, FH Tyler. J Clin Invest. 1972 Aug; 51(8):2040-6.

[9] The parathyroid hormone circadian rhythm is truly endogenous--a general clinical research center study. G el-Hajj Fuleihan , EB Klerman , EN Brown , Y Choe , EM Brown , CA Czeisler. J Clin Endocrinol Metab. 1997 Jan; 82(1):281-6.

limited utility versus if the sponsor had attempted a mechanistic model to relate these markers.

- Effect of Natpara on reduction in urinary calcium excretion is short-lived (10-12 hours for 50 and 100 µg doses upon short-term and long-term use). This is full concordance with the Natpara PK profile, where, the concentrations return to baseline by 12 hours. This could also be the artifact of saturation of the renal active transport system by the increased filtered load of calcium, which triggered by the PTH effect on increased serum calcium in the first-half of the 0-24 hour duration.

PK and PD principles and their significance in the design of a successful drug therapy become even more critical when dealing with endocrine hormones, such as PTH, due to multiple physiological mechanisms that get affected by them and integrated nature of these mechanisms within the endocrine system in facilitating the treatment response. The importance of these principles to Natpara is described below. General clinical pharmacology information is located in Appendix 3.1.1 of this document.

Single escalating dose PK/PD in patients with hypoparathyroidism (CL09-002):

This study captured the short-term effects of Natpara administration in patients with hypoparathyroidism on the PD markers of interest, following the SC injection of Natpara in the thigh.

Key Observations for Natpara PK:

- Plasma rhPTH[1-84] levels increased rapidly resulting in a double peak concentration profile: an initial peak occurred at 5 – 30 min and a second usually smaller peak at 1 – 2 hours after the injection.
- The mean (SD) baseline adjusted C_{max} was 174 (50) and 233 (126) pg/mL and the baseline adjusted mean (SD) AUC_{0-24} was 572(123) and 924(175) pg*hr/mL with the 50 µg and 100 µg doses, respectively.
- Natpara has a half-life of about 3 hours with both doses, with mean plasma rhPTH[1-84] levels returning to pre-dose levels by 10-12 hours post-dose.

The mean (±SE) plasma concentration-time profiles of rhPTH[1-84] after a single SC doses of 50 or 100 µg are illustrated in Figure **4** below.

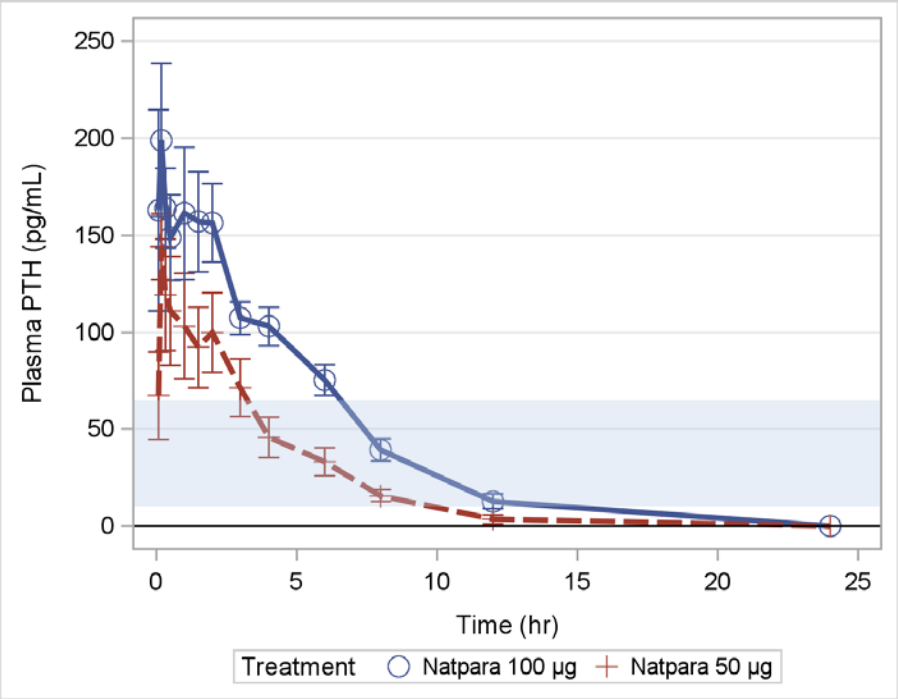


Figure 4 Mean plasma concentration versus time profile of Natpara (single 50 and 100 µg SC doses in the thigh of same subjects, minimum 7 days washout between 2 periods)

Key Observations for Natpara Pharmacodynamics: The PD effects are described in the terms of effects of rhPTH[1-84] on serum calcium, serum 1,25$(OH)_2$D levels, and urinary calcium excretion. Additional effects on urinary cyclic-AMP, serum and urinary phosphate, serum and urinary magnesium, etc. are presented in Appendix 3.1.2.

Serum calcium:

- After the oral administration of calcitriol, mean increase in baseline-adjusted albumin-corrected serum total calcium levels of approximately 0.4 to 0.5 mg/dL occurred at about 12 hours
- Following rhPTH[1-84] injection, there was a dose-related increase in albumin-corrected serum total calcium levels in each period (Figure 5). The maximum mean increases, which also occurred at 12 hours, were approximately 0.6 mg/dL and 0.8 mg/dL, with the 50 µg and 100 µg doses, respectively.

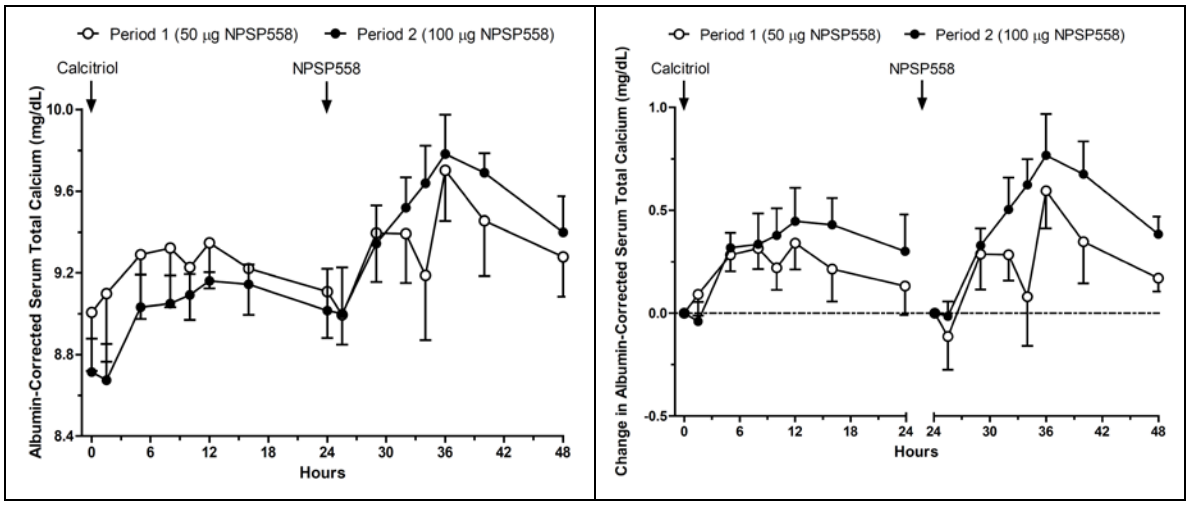


Figure 5 Mean (±SE) actual (left) and baseline adjusted (right) albumin-corrected serum calcium versus time profile with calcitriol or Natpara 50µg (left) and calcitriol or Natpara 100 µg SC treatments

Serum 1,25(OH)D Levels: Mean(±SE) baseline-adjusted serum $1,25(OH)_2D$ concentrations during Period 1 (50 µg NPSP558) and Period 2 (100 µg NPSP558) are shown in Figure 6 below overlaid on profiles after calcitriol administration on the corresponding Day -1 of each period.

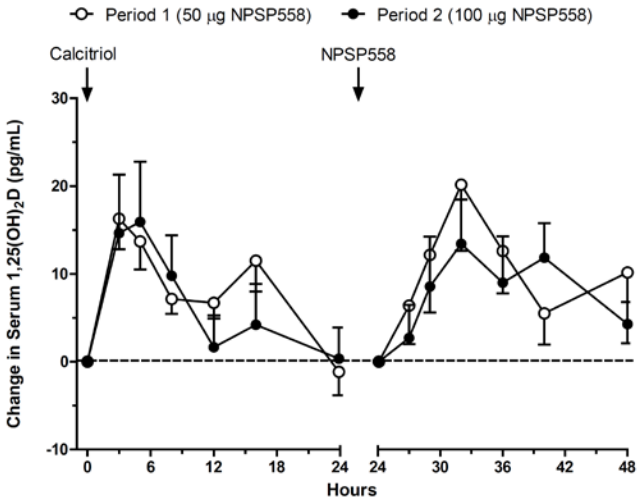


Figure 6 Mean (±SE) serum $1.25(OH)_2D$ versus time profile with calcitriol (left) and rhPTH[1-84] (right) 50 µg (○) and 100 µg (●) SC treatments

- The median time of the maximum increase (15 to 20 pg/mL with calcitriol/Natpara) in serum $1,25(OH)_2D$ following oral calcitriol administration was 3 - 5 hours whereas it occurred at 8 – 16 hours following Natpara injection, respectively.
- The mean net AUC on baseline-adjusted serum $1,25(OH)_2D$ following calcitriol administration were 182 and 144 pg*h/mL in Period 1 and Period 2, respectively. On average, the AUC tended to be higher following rhPTH[1-84] administration (232 and 199 pg*h/mL, respectively, with the 50 µg and 100 µg doses. However, effect on serum $1,25(OH)_2D$ showed lack of dose-response (Figure 7).

Effect on Urinary PD Markers: Timed urine samples were collected throughout each study day for cyclic AMP, calcium, magnesium, phosphate and creatinine concentrations. The collection intervals were the same on Day -1 and Day 1 within each period. For each sample, the total amount of each analyte excreted was calculated and the amount excreted over the entire 24 hours was determined. The fractional excretion (FE) of calcium, magnesium and phosphate were determined. FE is defined as clearance of the analyte divided by the glomerular filtration rate (GFR) and thus represents the percentage of each analyte filtered at the glomerulus. Creatinine clearance was used as a measure of GFR.

Calcium Excretion:

- The pattern of fractional excretion of calcium (FE_{Ca}) was very similar following oral calcitriol administration in Period 1 and Period 2. When rhPTH[1-84] was administered there was an immediate decrease in FE_{Ca} to a nadir in the 3 – 6 hour urine sample. When compared with the level observed in the 16 – 24 hour urine sample on Day -1, the magnitude of the maximum decrease in FE_{Ca} was very similar with both the 50 μg (68% decrease) and 100 μg (65% decrease) doses of rhPTH[1-84]. Thereafter, the FE_{Ca} increased progressively towards pre-dose levels. The rate of restoration to predose levels occurred more rapidly with the lower dose of rhPTH[1-84], but FE_{Ca} levels in the 16 – 24 hour sample after rhPTH[1-84] administration were very similar to those in the same urine sample on each Day -1.
- Total 24-hour urinary calcium excretion was very similar on each Day -1. Treatment with rhPTH[1-84] reduced mean total calcium excretion by 13% (380 to 330 mg) and 23% (373 to 286 mg) with the 50 μg and 100 μg doses, respectively.

To further understand the calcium sparing effect and the role of urinary excretion changes, the urinary excretion data was analyzed using non-compartmental analysis (WinNonlin module in Phoenix®; Pharsight Corporation) to compute the calcium excretion rate by mid-point of collection interval. Reviewer's analysis of urinary excretion data is presented in Figure 9 below.

Depending upon the reference point, this data reveals different magnitude of effect on urinary calcium excretion. For instance, sponsor compared the data over 0-3h interval with PTH treatment to 16-24h interval with the calcitriol treatment that preceded the PTH treatments. In contrast, when all the excretion profiles are overlaid, the excretion rate over 0-3h interval does not differ across 4 treatment visits. The 0-3h collection interval data from the calcitriol treatment visits seems to be a reasonable baseline as subjects were on a stable calcium and calcitriol dose in the study. There is a reduction in calcium excretion rate during the 3-6 hour collection, which gradually rises to the magnitude seen with calcitriol treatment by 12 hours. This reveals that the duration of rhPTH[1-84] action on reduction in urinary calcium excretion is short-lived (10-12 hours for 50 and 100 mcg dose). These effects are in accordance with the observed PK profile, where, the rhPTH[1-84] concentrations return to baseline by 12 hours.

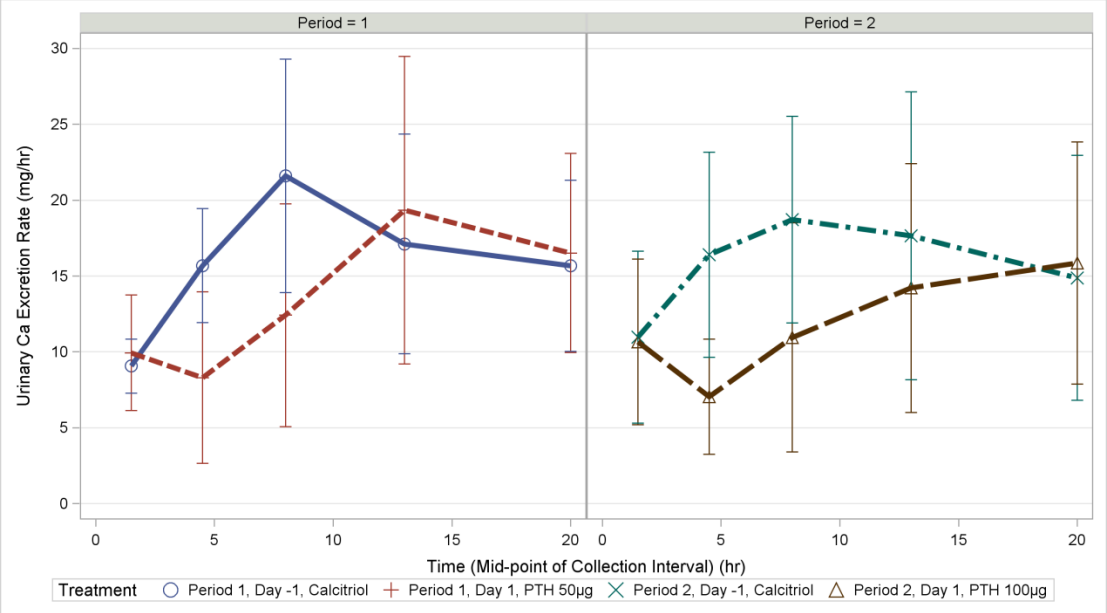


Figure 7 Mean urinary excretion rate of calcium versus time by visits specific for calcitriol (○ and X) and rhPTH[1-84] 50 µg (+) and 100 µg (Δ) SC treatments

<u>Mosekilde-IIT PKPD sub-study in Patients with hypoparathyroidism:</u>

This study captured the effects of rh-PTH administration after long-term use (last day of 100 µg SC QD for 6 months) in patients with hypoparathyroidism on the PD markers of interest. This was a 1-day pharmacokinetic/pharmacodynamic (PK/PD) study, conducted on the last day of the 24-week, randomized, double-blind, placebo-controlled, parallel-group IIT in subjects with hypoparathyroidism receiving active or native vitamin D and calcium supplementation.

Subjects fasted on the morning of their last study day of the IIT. Following a morning SC injection of 100 µg of rhPTH(1-84) or placebo in the thigh, blood sampling for determination of plasma rhPTH(1-84), total calcium, albumin, magnesium, and phosphate, as well as urine collection for total calcium, magnesium and phosphate were performed at specified intervals from baseline through 24 hours.

Mean (95% confidence bands) plasma concentration-time profile of PTH, total vitamin D (calcitriol), serum calcium, 24-hour urinary excretion (median), and serum phosphate after multiple once daily SC administration of placebo (top) or 100 µg rhPTH[1-84] dose in the thigh (assessed on last day of 24 week treatments) are presented in Figure 8 below.

The pharmacokinetics of rhPTH[1-84] was similar after administration of a single 100 µg dose and after multiple doses at steady-state on last day of 6 month treatment with QD regimen. Following SC administration, peak levels reached at approximately 0.4 h after dosing. Plasma concentration-time profiles showed a monophasic decline with mean terminal elimination half-life of 2 hours. Consistent with the half-life, no accumulation was observed at steady-state.

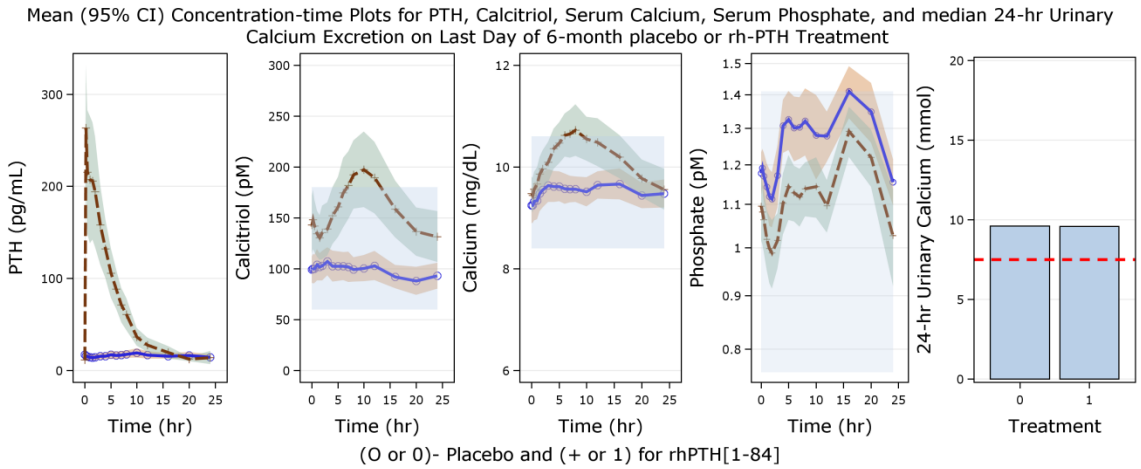


Figure 8 Mean (95% confidence bands) plasma concentration-time profile of PK – (endogenous/exogenous PTH) and PD – total vitamin D (calcitriol), serum calcium, serum phosphate, and 24-hour urinary excretion (median) after multiple once daily SC administration of placebo or 100 µg rhPTH[1-84] dose in the thigh (assessed on last day of 24 week treatments; shaded area represent normal ranges)

Actual and baseline-adjusted mean Cmax concentrations of rhPTH(1-84) in plasma were relatively similar (228 pg/mL and 210 pg/mL, respectively). Drug exposure (AUC0-last) derived from unadjusted and baseline-adjusted concentrations were 1311 pg*h/mL and 950 pg*h/mL, respectively. Clearance (CL/F), half-life (t1/2), and apparent volume of distribution (Vz/F) of rhPTH(1-84) were 89.0 L/h, 2.00 h, and 256 L, respectively. These parameters were comparable to those observed in C09-002 study. Although, a high degree of variability (CV%>30) was apparent in rhPTH[1-84] CL/F and Vd/F in this study.

rhPTH[1-84] PD: The PD effects are described in the terms of effects of rhPTH[1-84] on serum calcitriol, urinary calcium excretion and translational aspects on serum calcium and summarized in Figure 8.

According to the sponsor's conclusions, plasma concentrations of calcium, albumin-corrected calcium, and magnesium reached a peak at approximately 8 hours after rhPTH[1-84] administration then returned to approximately baseline levels at the 24-hour time point. Plasma phosphate concentration decreased in the first 2 hours after rhPTH[1-84] administration, then increased over the 24-hour period before returning to approximately baseline level at 24 hours, probably due to the ingestion of alphacalcidol during the PK/PD assessment day. In subjects receiving placebo, no clear relationship between plasma PTH(1-84) concentrations and PD biomarkers in plasma was evident, probably due to the intermittent ingestion of calcium and alphacalcidol by all placebo-treated subjects.

However, data clearly demonstrates that PTH administration on top of background calcium and vitamin D administration attains serum calcium that are towards the high end of upper limit of normal (ULN=2.65 mmol) although, the increase was approximately 0.3 mg/dL from baseline. Since subjects were taking alphacalcidol it is difficult to tease out the trophic effect of PTH on calcitriol, the fact that rhPTH[1-84] treated subjects were at

a higher baseline of Vitamin D than placebo subjects shows that rhPTH[1-84] must have exerted the trophic effect on 1-alpha-hydroxylase. Notably, alphacalcidol does not depend on the renal activation and rather activated by hydroxylation in liver[10]. Although, not mentioned in the study reports, the publication based on this study by Sikjaer et al[11] documented that subjects took variety of Vitamin D preparations, which makes the interpretation of Vitamin D levels difficult.

Effect on Urinary PD Markers: Timed urine samples were collected throughout each study day for calcium, magnesium, phosphate and creatinine concentrations. Sponsor concluded that urinalysis conducted during the study did not produce meaningful results.

However, Agency's analysis of urinary calcium excretion data (WinNonlin Module in Pheonix; Pharsight) reveals that there was a short-term decrease in the excretion rate of calcium from baseline in the 2-4 hours collection interval, which subsequently returned to baseline (similar to placebo value as well) by 10-12 hours (Figure 9). This was very much consistent with the observations from C09-002 study.

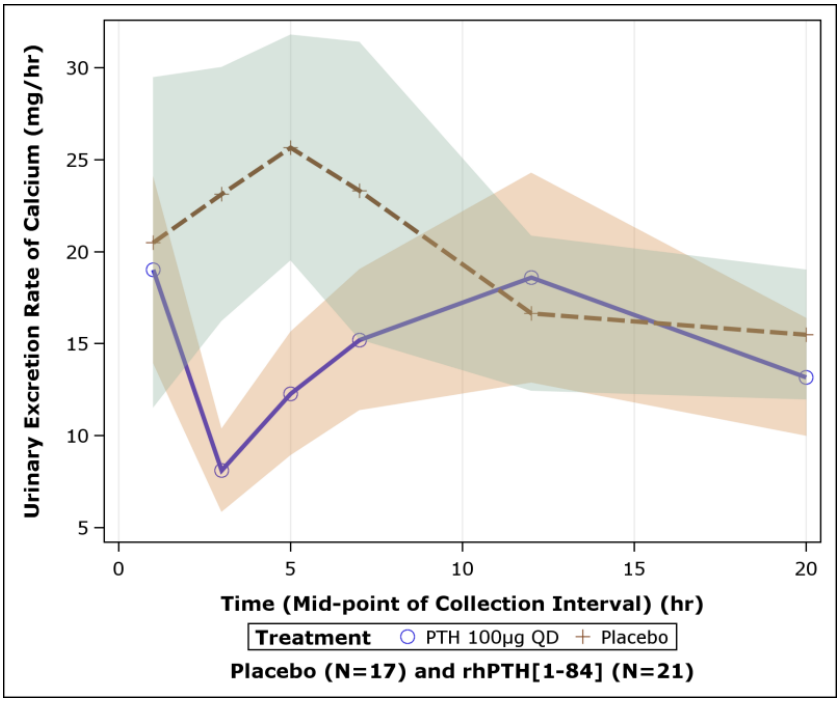


Figure 9 Mean (95% confidence) urinary excretion rate of calcium versus time on last day of 6 month placebo (+) and rhPTH[1-84] 100 µg (○) QD SC treatments

The median 24-hour calcium excreted in urine (402 mg/day exceeding the ULN of 300 mg/day) was similar between placebo and rhPTH[1-84] treatment groups. Since PTH

[10] Superiority of alfacalcidol compared to vitamin D plus calcium in lumbar bone mineral density in postmenopausal osteoporosis. Nuti R, Bianchi G, Brandi ML, Caudarella R, D'Erasmo E, Fiore C, Isaia GC, Luisetto G, Muratore M, Oriente P, Ortolani S. Rheumatol Int. 2006 Mar;26(5):445-53. Epub 2005 Nov 10.

[11] The effect of adding PTH(1-84) to conventional treatment of hypoparathyroidism: a randomized, placebo-controlled study. Sikjaer T, Rejnmark L, Rolighed L, Heickendorff L, Mosekilde L, and the Hypoparathyroid Study Group. J Bone Miner Res 2011; 26:2358–2370.

treatment group attained a higher peak serum calcium level than placebo amidst comparable baseline, the similarity in cumulative amount excreted in urinary excretion and urinary excretion rate data shows that the 100 µg QD dose is not able to provide a control on the urinary excretion beyond 10-12 hours over 24 hour duration.

Natpara effect on reduction of urinary calcium excretion is, therefore, short-lived (~10-12 hours for 50 and 100 mcg dose). The apparent short-lived effect on reduction in urinary excretion of calcium is a combination of several factors. While the non-genomic nature of rhPTH[1-84] response is one factor, the rise in calcium due to PTH stimulated influx of calcium from other sources (e.g. gut and bone) can drive the excretion rate up again in absence of adequate PTH levels to control urinary excretion of calcium. This is evident from the observed data as calcium urinary excretion rate peaked in 12-16 hour collection interval (Figures 7 and 9), and in serum peak calcium concentration occurred at 12 hours followed by a steady fall (Figures 5 and 8).

2.3 Degree of support from PK/PD and efficacy/safety data for the proposed QD administration of Natpara in Patients with hypoparathyroidism

Based on the review of PK/PD profile of Natpara, efficacy/safety results from the registration trial, it is likely that a lower and more frequent dosing regimen than QD or a QD dosing regimen with slow release formulation will likely provide a better control on hypercalciuria. The reviewers believe that adequate understanding of the reasons behind hypercalciuria and possible mitigation of this safety concern is essential for Natpara. Hypercalciuria is one of the primary safety concerns for the conventional therapy that results from using higher than usual calcium and vitamin-D doses. Therefore, the dose regimen should be further optimized to address the safety concerns for hypercalciuria.

The efficacy and safety of rhPTH[1-84] was evaluated in a randomized, double-blind, placebo-controlled, Phase 3 study in adult subjects with hypoparathyroidism. In brief, the proposed dosage regimen was adequate in reducing the calcium and vitamin D dose requirement while maintaining the albumin corrected total serum calcium within the 8-9 mg/dL target, albeit closer to the upper target limit (Refer to Clinical Section of the FDA EMDAC briefing document for further details). However, mean 24-hour urinary calcium excretion remained above the ULN (300 mg/day in males or 250 mg/day in females) with the rhPTH[1-84] treatment versus placebo (standard of care) where, at mean level 24-hour urinary calcium excretion remained within the normal range 50-300 mg/day).

Hypercalciuria: Safety aspect of Once Daily regimen

Based on the efficacy/safety results from the registration trial along with the PK/PD information of Natpara (C09-002 and Mosekilde-IIT), Natpara doses up to 100 µg once daily do not provide optimal control on the excretion of calcium in urine in all subjects. PKPD data reveals that this is primarily due to short half-life (~ 3 hours) of Natpara which results in PTH concentrations returning to baseline by 10-12 hours, similar to what sponsor have acknowledged in the clinical pharmacology summary document that PD effect on serum calcium are dependent on duration of exposure rather than magnitude of exposure.

It is important to note that the proposed Natpara dosage regimen was adequate in reducing the calcium and vitamin D dose requirement while maintaining the mean

albumin corrected total serum calcium within the 8-9 mg/dL target, albeit closer to the upper target limit.

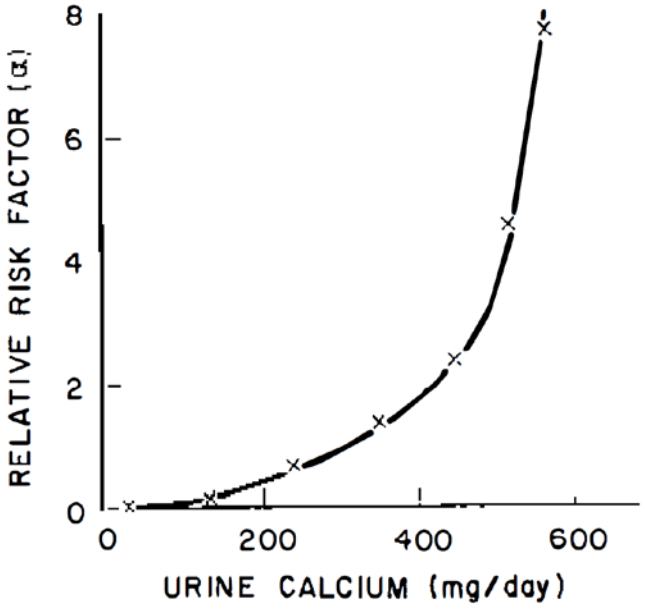


Figure 10 Relative risk of calcium stone formation at any given level of calcium excretion (Figure sourced from Stewart and Broadus. Ann. Rev. Med. 1981. 32: 457-73.)

Excessive calcium excretion in urine is considered as a risk factor for renal damage with the conventional treatment of hypoparathyroidism with high calcium and vitamin D doses. Stewart and Broadus and Pak et al[12] reported quantitative threshold for hypercalciuria that is associated with increased risk of nephrolithiasis in general population. Their analysis showed the optimal cutoff point for urinary calcium excretion was 172 mg/day on a restricted diet (a value that approximates the traditional limit of 200 mg/day) at which, a clear demarcation was seen between urinary calcium excretion of kidney stone formers with absorptive hypercalciuria type I and normal individuals.

It was observed that with rhPTH[1-84] treatment, the mean 24-hour urinary calcium excretion was higher than ULN. It is worth noting that the 24-hour urinary calcium excretion data was not available at intermediate visits for all subjects (see datalabels in Figure 11). However, with this caveat in mind the data in hand was further analyzed to assess the extent of hypercalciuria in the Phase 3 trial population to understand this safety aspect of Natpara dosing regimen.

Figures 11 present the proportion of 24-hour urinary calcium excretion values that matched the criteria for hypercalciuria (>300 mg for males and >250 mg for females[13]) at each visit by treatment over duration of trial. In Figure 12, corresponding Mean (95% confidence band) 24-hour urinary calcium excretion in normocalciuria and hypercalciuria

[12] Charles Y.C. Pak et al. Defining hypercalciuria in nephrolithiasis. Kidney International (2011) 80, 777–782.

[13] Phillip M. Hall. Nephrolithiasis: Treatment, causes, and prevention. Cleveland Clinic Journal of Medicine Vol 76(10) 2009.

situations at each visit by treatment over duration of trial, respectively for Phase 3 trial CL1-11-040.

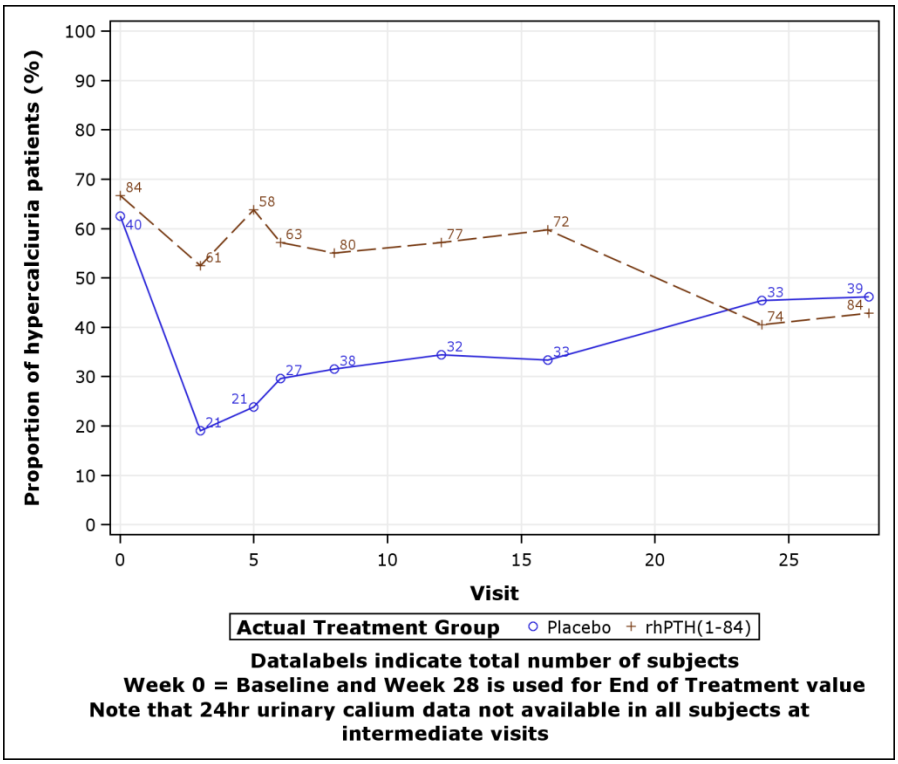


Figure 11 Proportion of subjects with hypercalciuria by treatment over duration of trial (Phase 3 trial CL1-11-040)

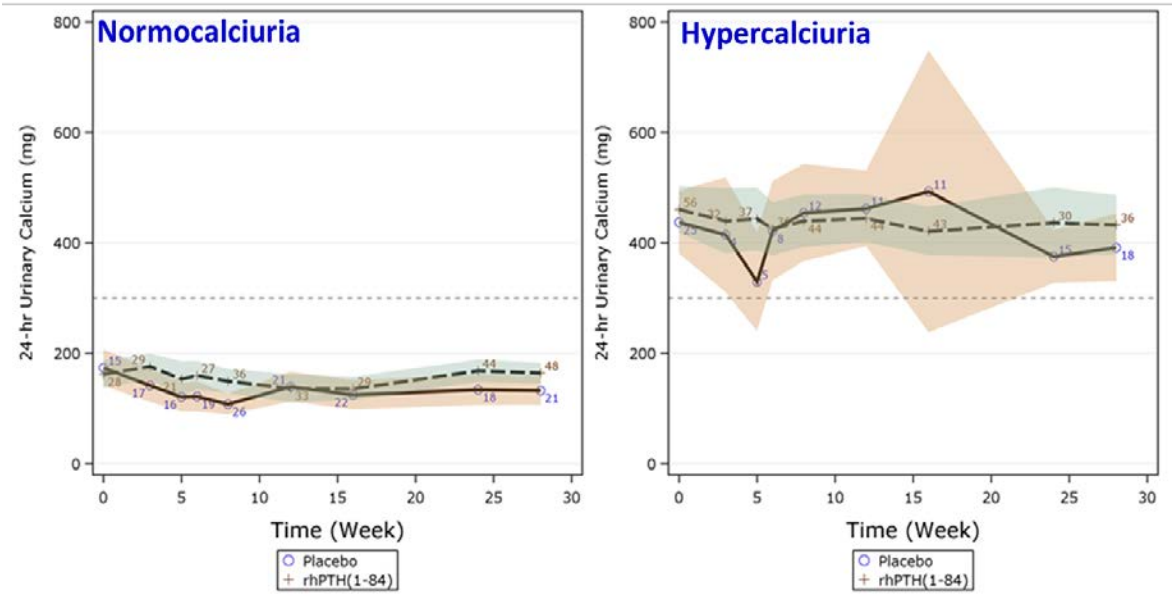


Figure 12 Mean (95% confidence band) 24-hour urinary calcium excretion in normocalciuria and hypercalciuria situations by treatment over duration of trial (Phase 3 trial CL1-11-040)

There was a trend for more hypercalciuria in rh[PTH] treatment than placebo similar to the trend indicated by the mean 24-hour urinary calcium excretion profile (Figure 11). The magnitude of 24-hour urinary calcium excretion was similar on average between placebo (standard of care) and rhPTH[1-84] treatments when the values were classified and summarized by normocalciuria or hypercalciuria (Figure 12). Furthermore, the mean urinary calcium did not increase over time in situations of normocalciuria or hypercalciuria. However, under hypercalciuria situations it implies that there was not much improvement with regards to reduction of hypercalciuria with Natpara treatment. This is an important finding as it does not align with the long term therapeutic goals of hormone replacement for hypoparathyroidism.

2.4 Need for further optimization of dosage regimen for Natpara in Patients with hypoparathyroidism

An alternate dosage regimen is required to optimize the safety and efficacy of Natpara specifically with regards to balancing serum calcium and 24-hour urinary excretion.

The results of projection conducted using a calcium homeostasis model demonstrate that a more frequent dosing regimen or a formulation with slow release profile will provide better control on hypercalciuria compared to the current once daily dosage regimen. The factors that may lead or could identify a patient's susceptibility to hypercalciuria during Natpara treatment need to be further investigated.

Potentially, one could utilize a mechanistic population PKPD analysis to explain the relationship between PTH PK – urinary calcium/phosphate excretion-serum calcium/phosphate profiles to get an answer to this question. However, considering that PTH has multifaceted effects that are mediated through several pathways, simultaneous modeling of such data, if not impossible, is a daunting task especially considering that there are three variables that changed in the clinical testing of the treatment: PTH, Calcium, and Vitamin D dose. A systems pharmacology approach was used since calcium homeostasis is affected by several factors including PTH, oral calcium, vitamin D, etc. and has several feedback mechanisms. The model is was intended to address the following:

- Adequacy of the model in describing PTH PKPD profile for both serum calcium and urinary calcium excretion simultaneously from a QD regimen.
- Capability of the model in evaluating alternate dosing scenarios (more frequent dosing or a QD dosing with slow release profile) from a PKPD perspective in the disease to determine if more frequent dosing regimen is optimal for controlling calcium excretion in urine. The intention of evaluating a more frequent dosing regimen or a regimen with slow release profile is to provide exposures for Natpara which are close to physiological levels along with adequate exposure coverage during the 24 hour period.

Systems Pharmacology Model:

There are a number of calcium homeostasis models available in the literature including a comprehensive minimal mathematical model of calcium homeostasis by Raposo et al[14]. We adapted a subsequent comprehensive model published by Peterson and Riggs (Implement in R and code available in public domain) for our purpose.

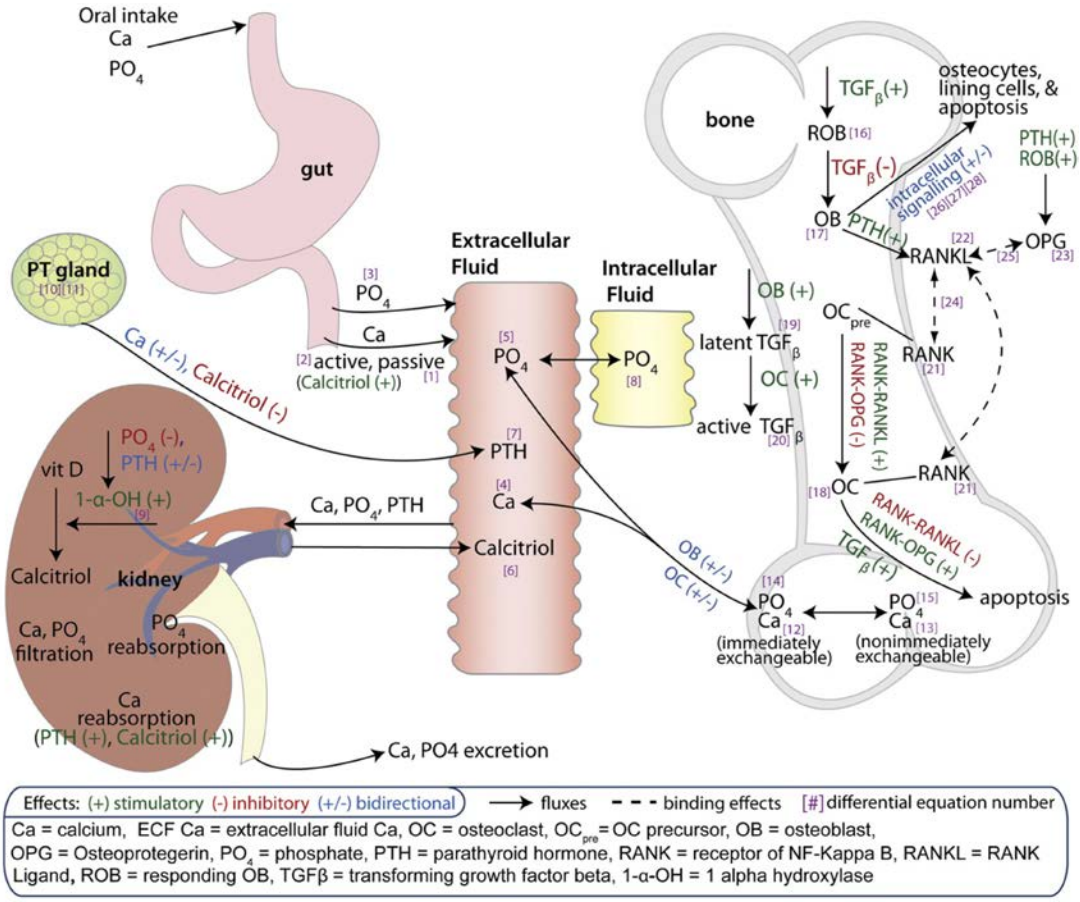


Figure 13 Schematic of the Calcium homeostasis model

This physiologic systems model combined three previously published models to include – (a) calcium homeostasis components, which describe the kinetics of serum calcium (Ca), phosphate (PO4), and relevant endocrine factors (PTH, calcitriol, 1-α hydroxylase and Parathyroid gland capacity [similar structural aspects as Raposo *et al*], (b) bone resorption and formation kinetics mediated by PTH, the RANK–RANKL–OPG axis, and TGF-β, and (c) osteoblastic intracellular signaling. Of note, the model included the renal calcium handling component [included expressions for both the filtered load and tubular reabsorption] that was defined having a 'renal threshold' for calcium, above which there is a linear increase in urinary calcium excretion with increased serum Ca concentration (See Figure 13).

[14] A Minimal Mathematical Model of Calcium Homeostasis. J. F. Raposo, L. G. Sobrinho, and H. G. Ferreira. J Clin Endocrinol Metab 87: 4330–4340, 2002

Our objective was to use a simulation based strategy in getting an answer to the above mentioned questions. We evaluated a modified version (Our modifications included rhPTH[1-84] PK, Vitamin D dose input, and 24-hour urinary excretion output) of Peterson and Riggs's model by simulating and graphical comparison to the external data available from this BLA submission (data that was not used for development of this model). A fit-for-purpose model validation strategy was adapted (see Figure 14). Upon gaining confidence in the model we simulated various 'what if' scenarios and compared it with the QD PKPD profile.

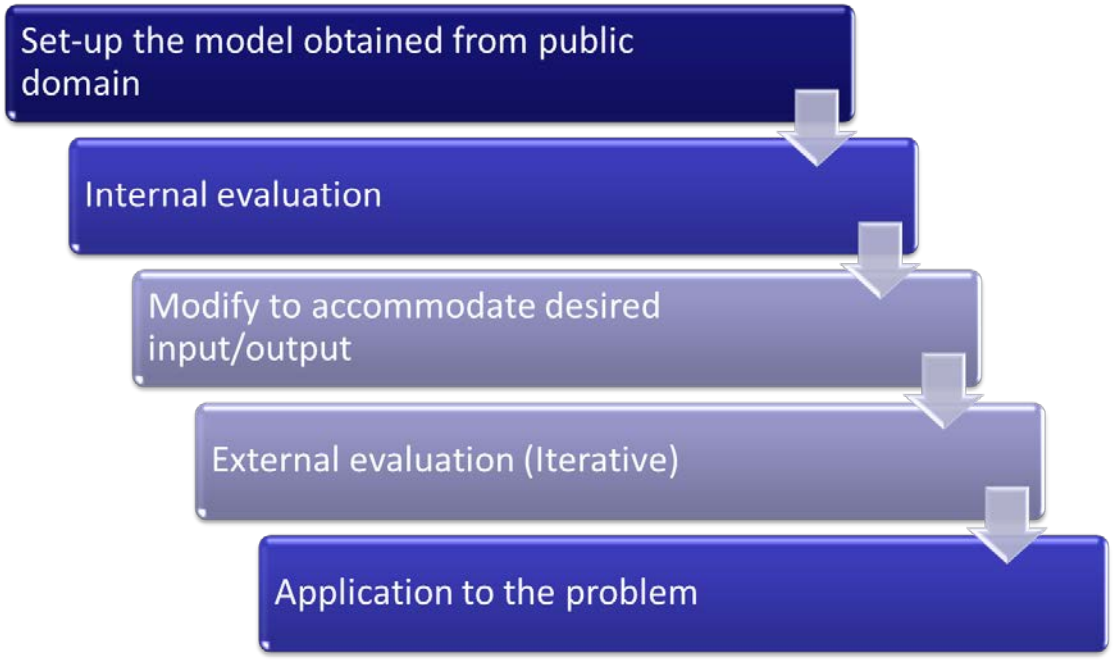


Figure 14 Schematic of the fit for purpose model validation strategy

Simulation for Hypoparathyroidism state:

Evaluation is an integral part of any model application, which is needed to develop confidence in the model that it can predict various 'what if' scenarios not directly evaluated in the clinical trials. Peterson *et al* used their model to demonstrate that their model was able to simulate a typical hypoparathyroidism patient (Primary hypoparathyroidism instituted in the model as an immediate 50% lowering of endogenous production of PTH from parathyroid gland).

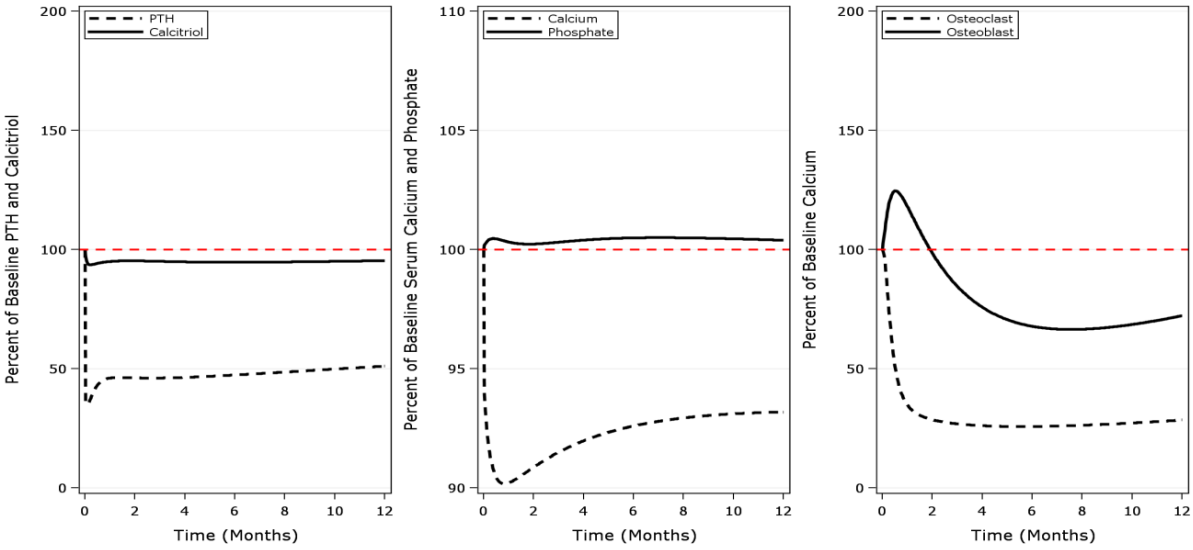
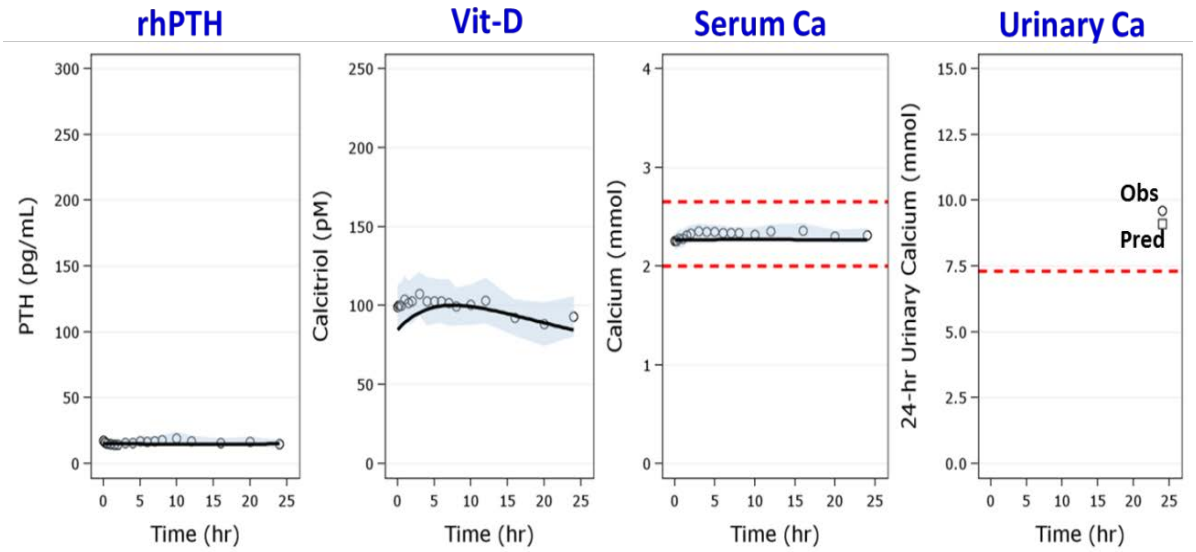


Figure 15 **Calcium homeostasis model has the capability to simulate the hypoparathyroidism disease state (reduction in circulating PTH and corresponding changes in serum calcium and osteoclast osteoblast activity)**

Using the publically available information, we implemented the model and confirmed that model was able to simulate a hypoparathyroidism state (Figure 15) and our results matched with what was reported in the publication. This constituted the internal evaluation of the model.

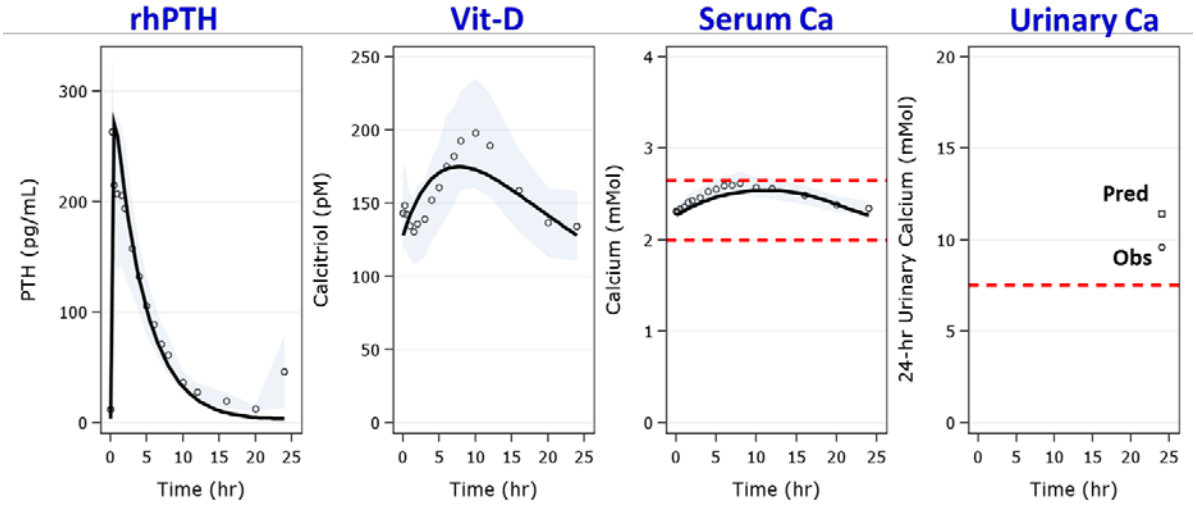
Following the internal evaluation, we performed external evaluation of the model, i.e., we used the model to predict placebo and rhPTH(1-84) PK, serum and urinary calcium output as PD effect and compared it with the observed data from the single dose (C09-002, Figure 25 and 26 in Appendix 3.1.3) and multiple dose (Mosekilde-IIT) PK/PD studies.

The model evaluation results using Mosekilde-IIT study are presented in Figures 16 and 17 below (see Appendix 3.1.3 for more results on model evaluation). Each figure presents the observed mean (95% confidence bands) and model projected (solid line) data for rhPTH, calcitriol, serum calcium, and 24 hour urinary excretion (cumulative amount) for the last day of 6-month QD treatment simulation with placebo (Figure 16) and rhPTH (Figure 17) indicating that model reasonably described the PKPD data observed in Mosekilde-IIT study.



Observed Mean(symbols with 95% confidence bands) and Predicted (solid lines) Concentration-time Plots for PTH, Serum Calcium, Calcitriol, and 24-hr Urinary Calcium Excretion on Last Day of 6-month Placebo Treatment
(Mosekilde-IIT, Modified Model)

Figure 16 Evaluation of model – model reasonably predicts the observed PK and PD data for placebo treatment in Mosekilde-IIT PKPD study. "Obs" implies Observed and "Pred" implies Predicted.



Observed (symbols) and Predicted (solid lines) Concentration-time Plots for PTH, Calcitriol, Serum Calcium, and 24-hr Urinary Calcium Excretion on Last Day of 6-month rh-PTH Treatment
(Mosekilde-IIT, Modified Model)

Figure 17 Evaluation of model – model reasonably predicts the observed PK and PD data for rhPTH[1-84] treatment in Mosekilde-IIT PKPD study. "Obs" implies Observed and "Pred" implies Predicted.

Simulation of Alternate Dosing Regimens

Once we established confidence on the model based on abovementioned internal and external model evaluations, simulations for QD, BID regimen and a QD regimen with slow release profile were conducted for various 'what if' scenarios and serum calcium

and 24-hour urinary calcium excretion profiles were compared versus the reference QD profile. The intent was to test the hypothesis that a more frequent administration (same total daily dose) or QD regimen with slow release profile will provide a better control on urinary calcium excretion while balancing serum calcium. We also compared the performance of these dosing regimens at two levels of PTH pool reduction: 50% and 99% reduction (both are clinically feasible situations).

The following scenarios were simulated using the validated systems pharmacology model for calcium homeostasis incorporating the rhPTH PK. To demonstrate the concept, the following simulations were conducted for a typical subject with the conditions described below:

Table 1 Overview of the projection scenarios using the systems pharmacology model for calcium homeostasis

Scenario #	Assumption of 50% loss in PTH gland pool (Similar to Mosekilde-IIT Population) 6 month treatment simulation			Assumption of 99% loss in PTH gland pool (Extreme Clinically Realistic Scenario) 6 month treatment simulation		
	PTH µg Dose (Frequency)	**Oral Ca (mmol/d)**	**Oral Calcitriol (µg)**	**PTH µg Dose (Frequency)**	**Oral Ca (mmol/d)**	**Oral Calcitriol (µg)**
1	100 QD	50	1.5	100 QD	50	1.5
2	50 BID	50	1.5	50 BID	50	1.5
3	100 QD	25	0.5	100 QD	25	0.5
4	50 BID	25	0.5	50 BID	25	0.5
Assuming a different slow release PK profile (1/10th absorption rate constant than current)						
5	50 QD	50	1.5	50 QD	50	1.5
6	50 QD	25	0.5	50 QD	25	0.5

The predicted serum calcium (mmol) and 24-hour urinary calcium excretion (mmol/day) for different dosing regimen is presented below in Figures 18 to 21 below. In the figures below, the shaded region in the left and middle plot represent the normal range of PTH and serum calcium, respectively, while the red dashed line in the plot on the right represents the ULN of 24 hour urinary calcium.

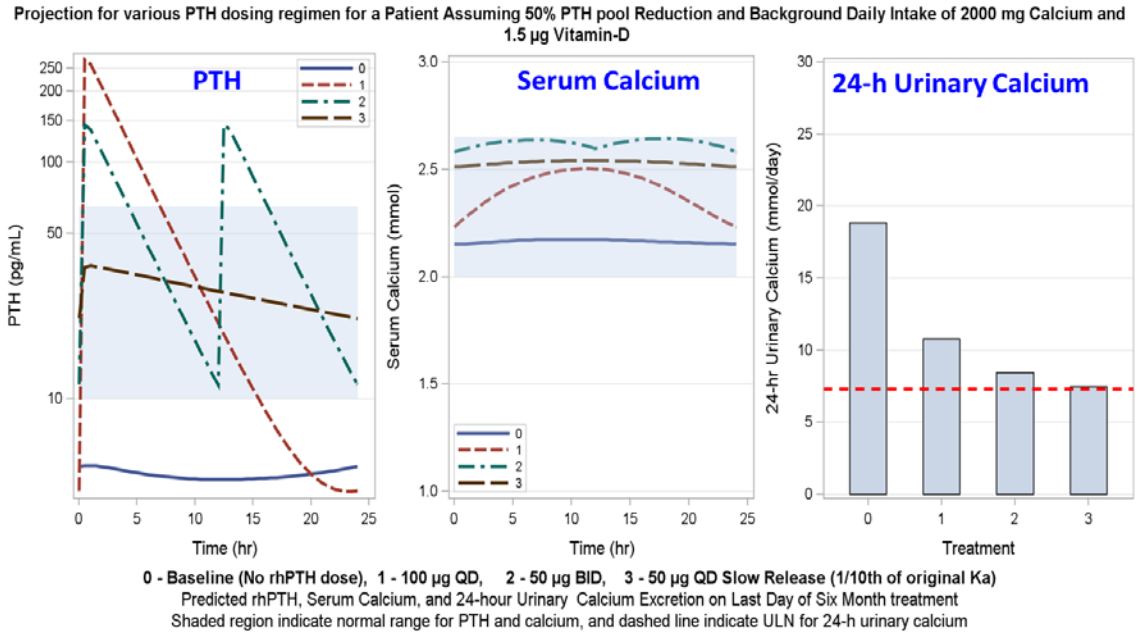


Figure 18 **Simulations show that 50 µg BID or 50 µg QD dose with slow release profile achieves better control on serum calcium and urinary calcium excretion versus 100 µg QD dose background intake of 1000 mg oral Calcium and 0.5 µg Vitamin in a patient representing 50% PTH pool reduction**

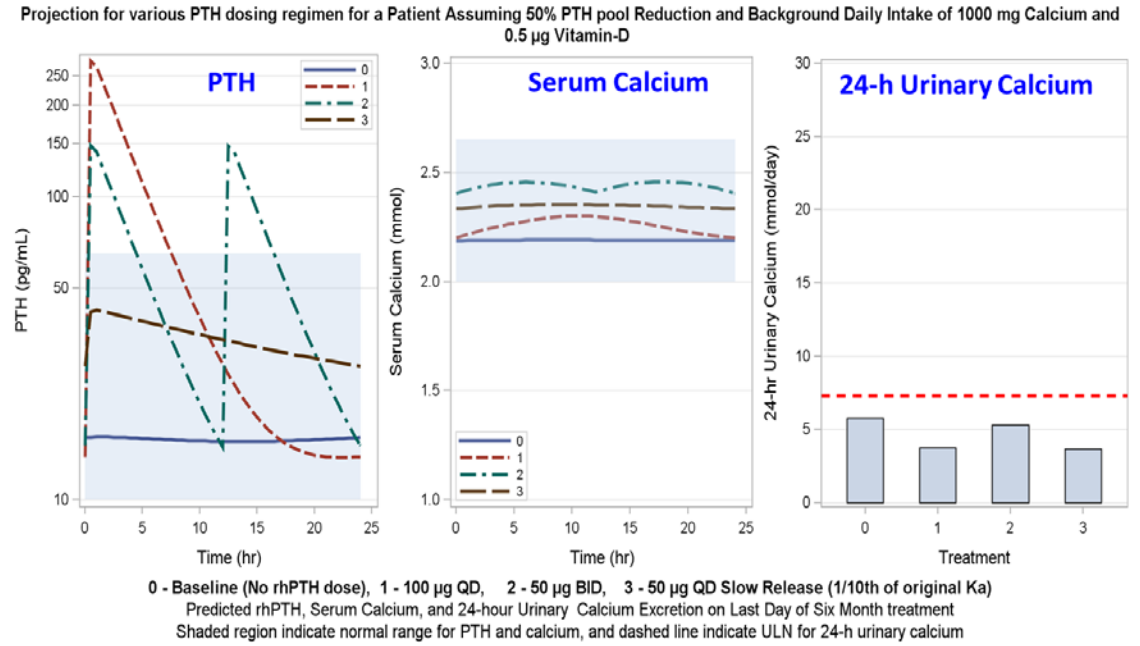


Figure 19 **Simulations show that 100 µg QD achieves better control on serum calcium and urinary calcium excretion versus 100 µg QD dose, however, or a slow release rhPTH profile achieves this target at 50 µg QD dose assuming background intake of 1000 mg oral Calcium and 0.5 µg Vitamin in a patient representing 50% PTH pool reduction**

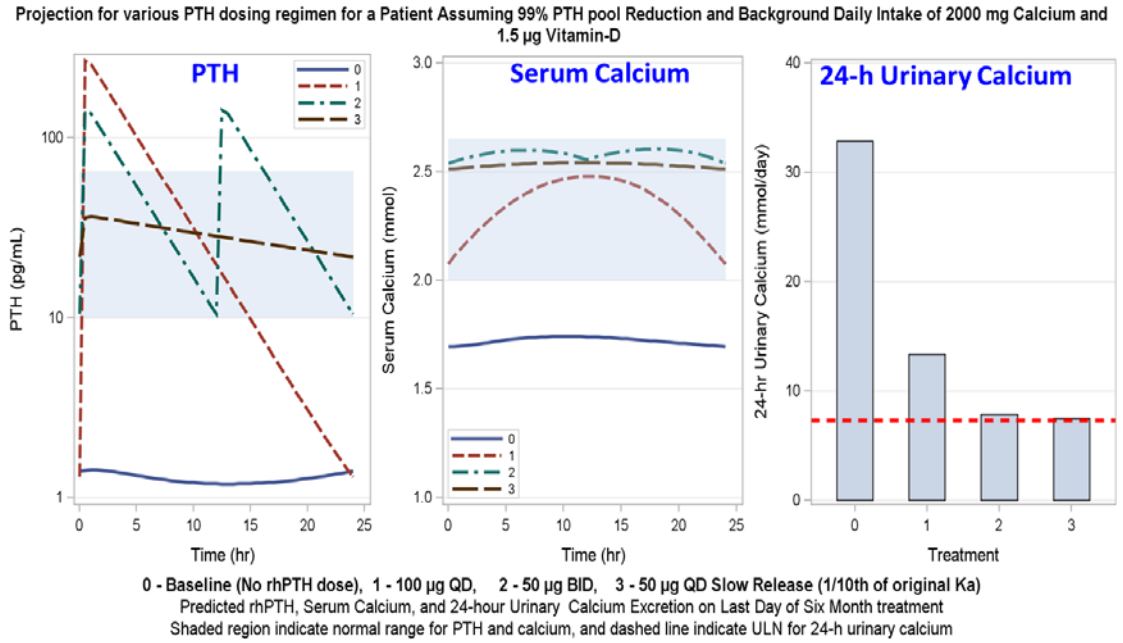


Figure 20 **Simulations show that 50 µg BID or 50 µg QD dose with slow release profile achieves better control on serum calcium and urinary calcium excretion versus 100 µg QD dose background intake of 2000 mg oral Calcium and 1.5 µg Vitamin in a patient representing 99% PTH pool reduction**

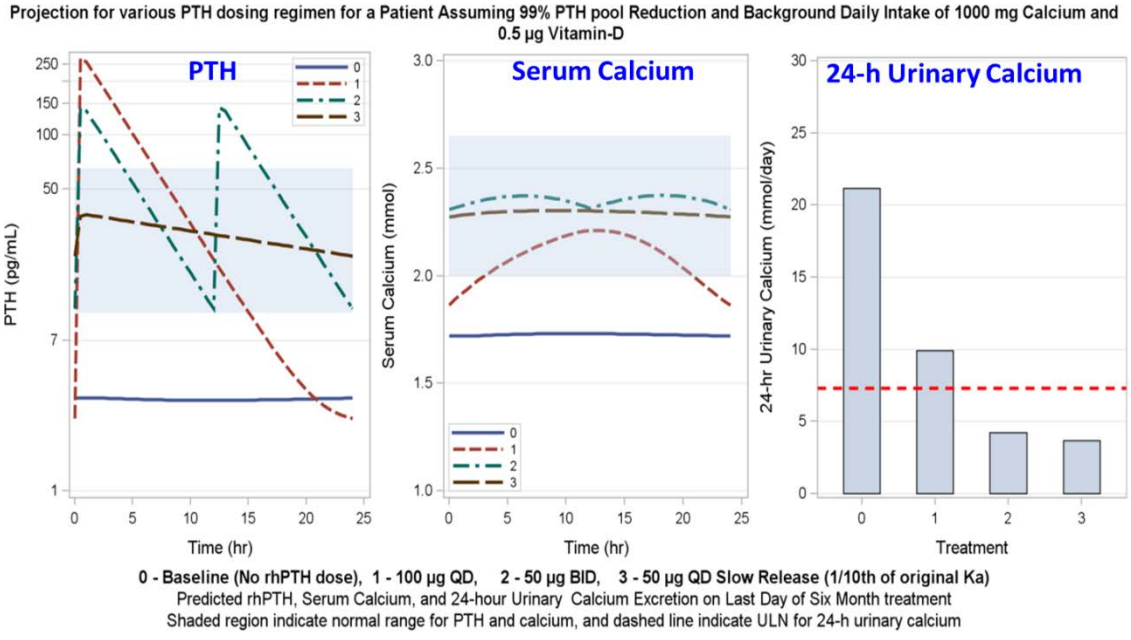


Figure 21 **Simulations show that 50 µg BID or 50 µg QD dose with slow release profile achieves better control on serum calcium and urinary calcium excretion versus 100 µg QD dose background intake of 1000 mg oral Calcium and 0.5 µg Vitamin in a patient representing 99% PTH pool reduction**

The simulations demonstrate that on average in a typical individual with normal renal function (GFR 100 mL/min) and on daily oral intake of 25 mmol (1000 mg) calcium and 0.5 µg calcitriol, it is feasible to achieve better control on 24 hour urinary calcium excretion (<7.3 mmol) and serum calcium (within normal range 2-2.65 mmol or 8.4-10.6 mg/dL) with more frequent administration of total daily dose of 100 µg, especially (50 µg BID) in both set of assumptions for 50% and 99% reduction of PTH pool. Further, under the assumption of a hypothetical product that provides slow release of PTH ($1/10^{th}$ the absorption rate constant of current formulation, this target was achieved at a lower 50 µg QD dose.

Limitations of the Simulation Exercise:

The simulations had some limitations as highlighted below:

- Simulations have not tested titration and rather tested one or two factors at a time (e.g. effect of one PTH dose level and daily calcium intake and Vitamin-D dose level).
- The simulations represent the data at mean level and do not incorporate or address the variability that might be introduced by the factors affecting rhPTH pharmacokinetics or factors that may influence the response. The model have the capability to test the extremes (e.g. we tried to test one of the variability component – degree of baseline PTH gland function, though not much is known about the true quantitative magnitude of this factor in the patient population; we simulated the data assuming either 50% loss of PTH gland function or 99% loss).
- Clinically, there is heterogeneity in the choice of Vitamin-D (e.g. calcitriol, calciferol, alphacalcidol or other analogs) that was used as standard treatment. However, the model operates on the assumption of systemic levels of calcitriol (either stimulated by PTH or from exogenous administration). It is unknown if all forms of Vitamin-D have similar inhibitory potential on residual PTH secretion or on stimulating the calcium reabsoprtion. It is beyond the scope of current model and simulations to account for these variations.

2.5 Published evidence on utility of alternate dosage regimen in management of patients with hypoparathyroidism

The pharmacologically active rhPTH[1-34] peptide has been evaluated by Karen Winer *et al*[2] in a randomized, controlled comparison of rhPTH(1-34) QD versus BID (0.7 µg/kg per day starting dose) in patients with Hypoparathyroidism. The study demonstrated that in patients with acquired or idiopathic hypoparathyroidism, serum calcium was maintained within the normal range (Figure 22). The total daily PTH dose was markedly reduced with the twice-daily regimen (twice daily 46±52 µg/day vs. once daily 97±60 µg/day, P<0.001).

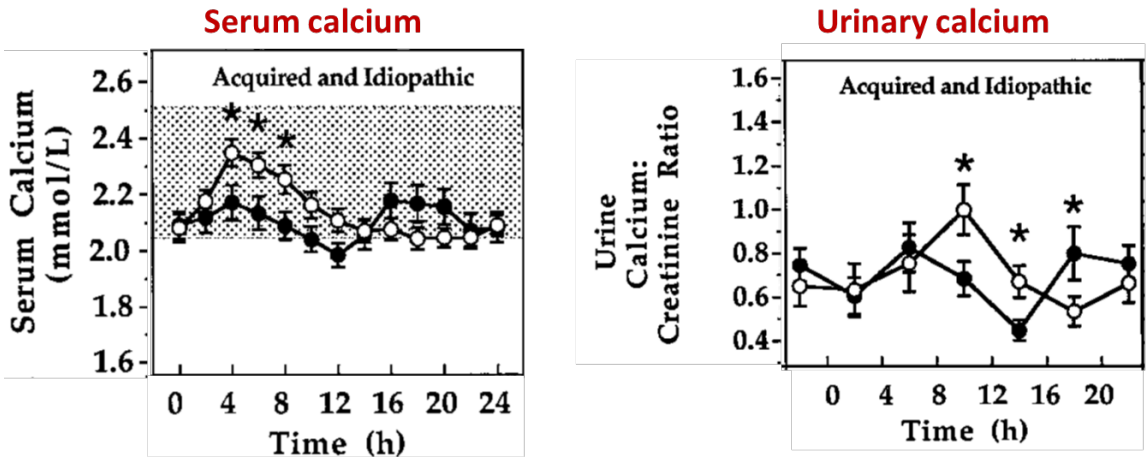


Figure 22 Mean (±SE) serum calcium and urine calcium/creatinine ratio with QD and BID regimen of rhPTH(1-34) (Figure Adapted from Karen K. WINER et al. J Clin Endocrinol Metab 83: 3480–3486, 1998)

In another study continuous SC infusion using a pump delivery was compared BID regimen of rhPTH(1-34).

The data demonstrated that both serum calcium and 24-hour urinary calcium excretion were controlled with the pump delivery in comparison to the BID regimen (see Figure 23). Mean±SD daily rhPTH(1-34) dose was 65% less during pump versus BID delivery (13±4 vs 37±14 µg/day, P<0.001).

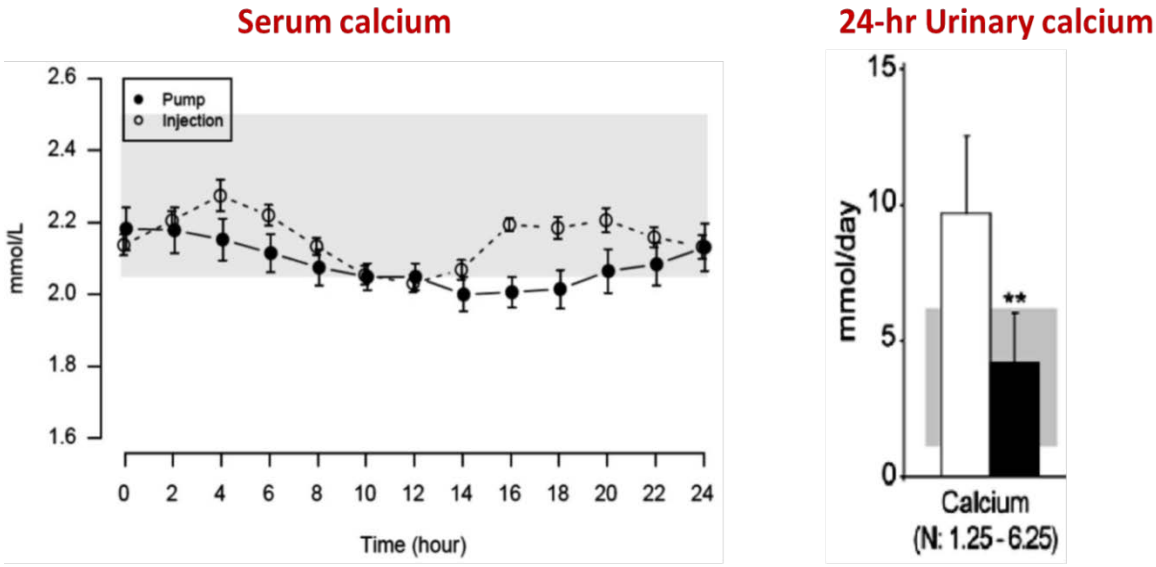


Figure 23 Mean (±SE) serum calcium and urine calcium/creatinine ratio with QD and BID regimen of rhPTH(1-34) (Figure Adapted from Karen K. Winer et al. J Clin Endocrinol Metab. 97: 391–399, 2012)

3 Appendix

3.1 Supplemental Information

3.1.1 General Clinical Pharmacology of Natpara

Absorption: The relative BA of Natpara Cmax and AUC are 30 – 43% and 16 - 21% lower, respectively, upon SC rhPTH injection in the thigh vs. those in the abdomen. The absolute bioavailability assessment for rh-PTH, available from SC injection in the abdomen is about 55%. The SC rhPTH pharmacokinetics (PK) is dose-proportional for the dose range of 0.5 to 5 μg/kg (35 – 350 μg for a typical 70 kg individual). Multiple SC rhPTH daily injections in the thigh do not lead to systemic PTH accumulation.

Distribution: The volume of distribution at steady-state is 3.8 – 7.3 L.

Metabolism and Excretion: The sponsor did not study rhPTH's human metabolism and excretion properties but a previous review captured the extensive published literature on this topic. Briefly, PTH metabolism is believed to occur enzymatically in the liver (non-specific) and then followed by excretion in the kidneys. Mean rhPTH terminal $t_{1/2}$ is 0.43 and 1.49 hour after intravenous (IV) and SC rhPTH administration, respectively. Hence, SC rhPTH administration shows flip-flop kinetics, i.e., primarily driven by the rate of absorption from SC injection site.

Removal of PTH (1-84) via the liver and kidney accounts for about 90% of its clearance and PTH (1-84) has a plasma $t_{1/2}$ of 2 – 5 minutes[15]. Liver's Kupffer cells metabolize PTH to different fragments such as the PTH (7-84) fragment[16]. The PTH (7-84) fragment may inhibit PTH (1-84) action. The amino-truncated PTH fragments are predominantly cleared via the kidneys.[17]

[15] Marcus. Agents affecting calcification and bone turnover. In: *Goodman and Gilman's- The Pharmacological Basis of Therapeutics,* 10th ed., 2001, pp 1722.

[16] Potts et al. Parathyroid hormone: chemistry, biosynthesis, and mode of action. *Ad Protein Chem.* 35: 323-96 (1982).

[17] Friedman. Agents affecting mineral ion homeostasis and bone turnover. In: *Goodman and Gilman's The Pharmacological Basis of Therapeutics,* Chapter 61, 11th ed., 2006.

3.1.2 Supplemental PKPD data from C09-002 and Mosekilde IIT Study

PK Parameters after single dose (C09-002 Study):

PK Parameter	Treatment			
	50 µg NPSP558 SC (N = 6)		100 µg NPSP558 SC (N = 7)	
	Arithmetic Mean	SD	Arithmetic Mean	SD
$AUC_{0\text{-last}}$ (pg·h/mL)	572	123	924	175
$AUC_{0\text{-}\infty}$ (pg·h/mL)	636	122	1016	177
C_{max} (pg/mL)	174	49.7	233	126
$t_{1/2}$ (h)	3.02	1.26	2.83	0.721
CL/F (L/h)	81.0	14.7	102	21.1
V_{ss}/F (L)	357	171	488	172
T_{max} (h)[a]	0.250 (0.167, 2.00)		0.167 (0.0833, 1.50)	

N=Number, SD=Standard Deviation, SC=Subcutaneous

[a] Median (minimum, maximum) is presented for T_{max}

PD - total serum calcium:

- Mean maximum increase in baseline-adjusted serum total calcium levels of ~0.4 to 0.5 mg/dL occurred at about 12 hours after the oral administration of calcitriol (0.5-0.75 µg) and calcium intake of ~2500 mg in each period (data not shown). On rhPTH[1-84] treatment days with similar average calcium intake but without calcitriol, there was a dose-related increase in serum total calcium levels following rhPTH[1-84] injection. The maximum mean increases which also occurred at 12 hours were approximately 0.5 mg/dL and 0.7 mg/dL, with the 50 µg and 100 µg doses of rhPTH[1-84], respectively.
- Mean (SD) net AUC (AUC_{above} – AUC_{below} baseline) for serum Ca increased in dose-dependent manner from 6.07 (6.25) with 50 µg to 11.4 (6.48) (mg*h/dL) with 100 µg dose. On corresponding calcitriol treatment visits (a day prior), the net AUC was 5.21 (5.63) and 7.63 (6.69) mg*h/dL) revealing that rhPTH[1-84] treatment contributed towards the serum calcium rise as calcitriol was not administered.

PD – Urinary Calcium, Phosphate, Magnesium and Cyclic-AMP:

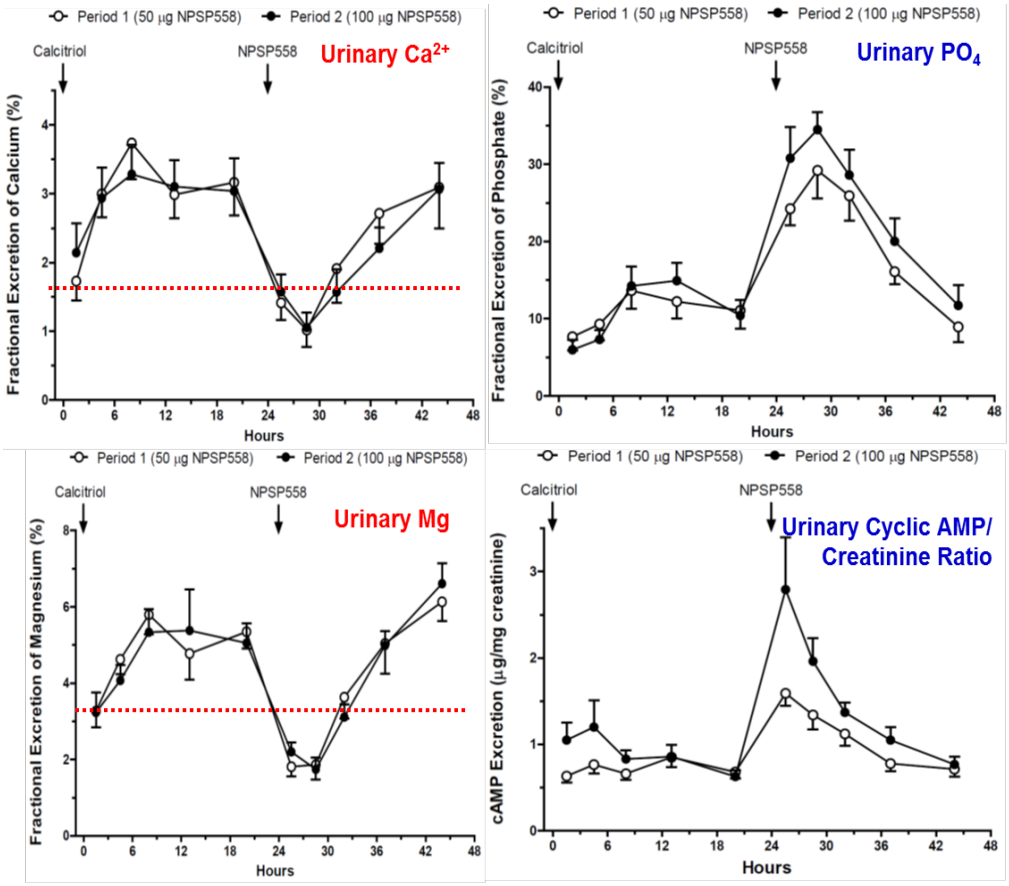


Figure 24 Mean (±SE) fractional excretion of urinary calcium (top left), phosphate (top right), magnesium (bottom left), and cAMP/creatinine ratio (bottom right) versus time profile with calcitriol and Natpara (NPSP558) 50 µg (○) and 100 µg (●) SC treatments

Cyclic AMP Excretion:

- Relative to calcitriol administration on each Day -1, administration of the 50 and 100 µg doses of rhPTH[1-84] increased total cyclic AMP excretion by 43% and approximately 59%, respectively, and cyclic AMP-to-creatinine ratio by approximately 38% and 66%, respectively.

PK after multiple QD dose:

The summary statistics of pharmacokinetic parameters for rhPTH[1-84] are presented in Table 2 below.

Table 2 Pharmacokinetic parameters of baseline-adjusted rhPTH[1-84] data on last day of multiple once daily SC doses of 100 µg over 24 weeks

PK Parameter	rhPTH(1-84) 100 µg SC (N = 22)
	Geometric mean (CV% geometric mean)
$AUC_{0\text{-last}}$ (pg•h/mL)	950 (93.2)
$AUC_{0\text{-}\infty}$ (pg•h/mL)	1124 (69.6)[a]
C_{max} (pg/mL)	210 (99.6)
$t_{½}$ (h)	2.00 (60.4)[a]
CL/F (L/h)	89.0 (69.6)[a]
V_z/F (L)	256 (130.4)[a]
	Median (min, max)
t_{max} (h)	0.36 (0.22, 2.08)

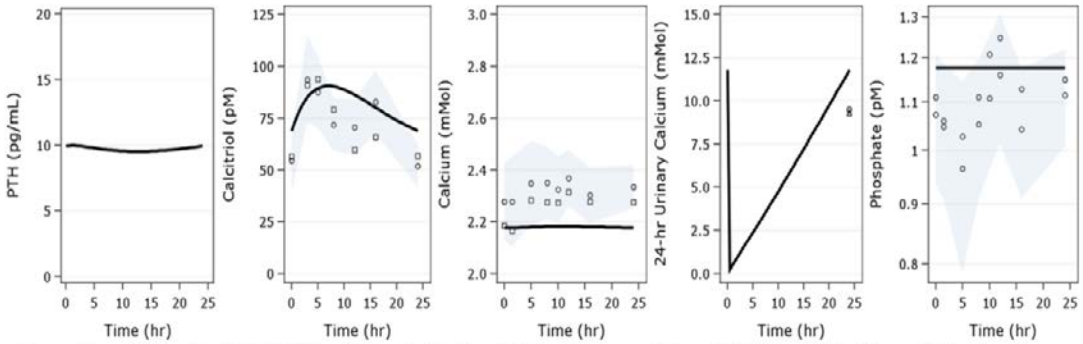
3.1.3 Supplemental data from simulations using the calcium homeostasis model

Model Evaluation Using Sponsor's PKPD study C09-002 study:

Assumptions:

- PTH treatments (single doses of 50 and 100 µg) were administered at steady-state of Hypoparathyroidism induction in the model (snapshot of last 4 days of 6 month treatment simulation).
- 60% reduction in PT gland pool and 50% reduction in max capacity.
- Calcium (2600 mg/day) continued throughout.
- Vitamin D as calcitriol (0.5 µg QD) initiated after 2 months and continued throughout.

Each figure presents the observed mean (95% confidence bands) and model projected (solid line) data for rhPTH, calcitriol, serum calcium, and 24 hour urinary excretion (cumulative amount) for placebo (Figure 25) and rhPTH (Figure 26).



Observed (symbols) and Predicted (solid lines) Concentration-time Plots for PTH, Serum Calcium, Calcitriol, and 24-hr Urinary Calcium Excretion on Day -1 (Calcium/Calcitriol Treatment)
(C09-002 PKPD, Modified Model)

Figure 25 Evaluation of model – model reasonably predicts the observed data for placebo treatment in PKPD study C09-002 (PTH were BLQ in placebo)

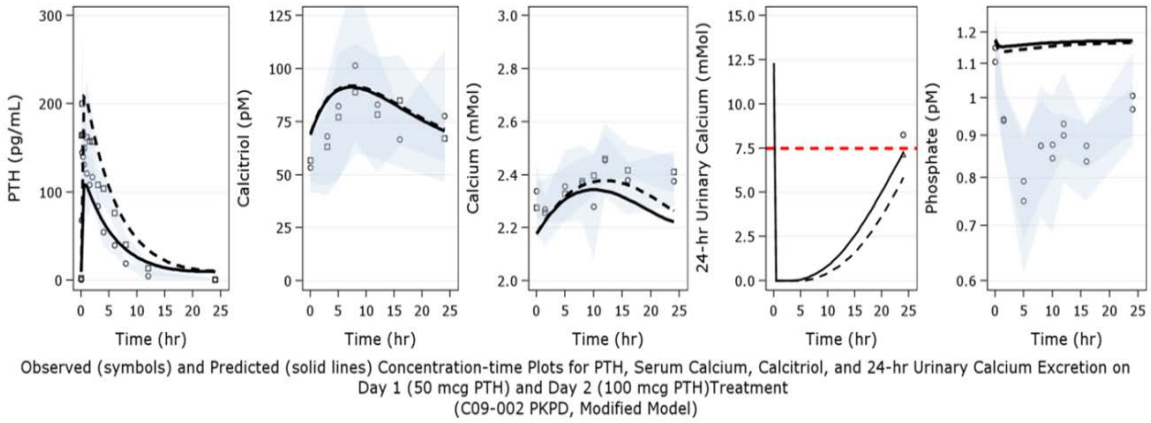


Figure 26 Evaluation of model – model reasonably predicts the observed PK and PD data for rhPTH[1-84] treatment in PKPD study C09-002

Assumptions for Simulations of Mosekilde-IIT study data:

Mosekilde-IIT PKPD sub-study in Hypoparathyroidism tested QD dose of 100 mcg rh-PTH on for 6 months versus placebo. Based on the publication[18] from this study, Placebo mean oral calcium intake was 1200 (range 800–3200) mg/day, Vitamin D as alphacalcidiol was [1.6 (0.25–3.5)] or calciferol was [33 (10–60)] µg/day. In the rhPTH arm oral calcium intake was 1600 (400–22,500) mg/day, Vitamin D as alphacalcidiol was [2.0 (0.25–42)] or calciferol was [20 (5–92)] µg/day.

Assumptions:

- 50% reduction in PT gland pool and 50% reduction in max capacity for steady-state of Hypoparathyroidism induction in the model (snapshot of last day of 6 month treatment simulation).
- Placebo - Calcium (2600 mg/day) and Vitamin D as calcitriol (0.5 mcg/day) continued throughout
- 100 mcg PTH - initiated after 1 month and continued throughout over 6 months and oral calcium (2200 mg/day) and Vitamin D as calcitriol (1.5 mcg/day)

The overview of results from model projections for several scenarios is summarized in Table 3 below. Our intent here is to demonstrate that conceptually with an alternate dosing regimen there are situations where both normocalcemia and normocalciuira is achievable.

[18] Sikjaer et al. Journal of Bone and Mineral Research, Vol. 26, No. 10, October 2011, pp 2358–2370

Table 3 Overview of the results from projection scenarios using the mechanistic calcium homeostasis model

Scenario #	Assumption of 50% loss in PTH gland pool (Similar to Mosekilde-IIT Population) 6 month treatment simulation			Assumption of 99% loss in PTH gland pool (Extreme Clinically Realistic Scenario) 6 month treatment simulation		
	PTH µg Dose (Frequency)	Oral Ca (mmol/d)	Oral Calcitriol (µg)/Duration (d)	PTH µg Dose (Frequency)	Oral Ca (mmol/d)	Oral Calcitriol (µg)/Duration(d)
1	0 QD	50	1.5	0 QD	50	1.5
2	0 QD	25	1.5	0 QD	25	1.5
3	0 QD	50	0.5	0 QD	50	0.5
4	0 QD	25	0.5	0 QD	25	0.5
5	100 QD	50	1.5	100 QD*	50	1.5
6	100 QD	25	1.5	100 QD*	25	1.5
7	100 QD	50	1.5 / 120 d	100 QD*	50	1.5 / 120 d
8	100 QD#	25	0.5	100 QD*	25	0.5
9	50 QD**	25	0.5	50 QD*	25	0.5
10	50 BID#	50	1.5	50 BID*	50	1.5
11	-			50 BID**	50	1.5 / 120 d
12	-			50 BID**	25	1.5 / 120 d
13	50 BID**	25	0.5	50 BID**	25	0.5
Assuming a different slow release PTH PK profile (1/10th absorption rate constant than current)						
14	-			100 QD*	50	1.5 / 120 d
15	100 QD	25	0.5	100 QD#	25	0.5
16	100 QD	25	0.5 / 120 d	100 QD#	25	0.5 / 120 d
17	50 QD**	25	0.5	50 QD**	25	0.5

d=days

Orange shades (*) indicate scenarios that projected decrease in calciuria but >ULN with/without normocalcemia. Green shades (**) indicate scenarios that projected normocalcemia and normocalciuria. Blue shades (#) indicate scenarios that projected calcium and calciuria in the proximity but below ULN. Remaining scenarios were projected as hypocalcemic/hypercaciuric.